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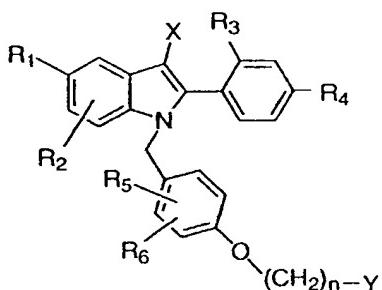
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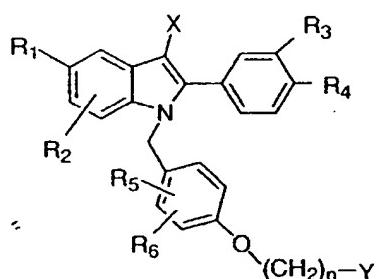
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(54) Estrogenic agents

(57) The present invention relates to new 2-Phenyl-1-[4-(2-Aminoethoxy)-Benzyl]-Indole compounds which are useful as estrogenic agents, as well as pharmaceutical compositions and methods of treatment utilizing these compounds, which have the general structures below:



or



Description

The present invention relates to new 2-Phenyl-1-[4-(2-Aminoethoxy)-Benzyl]-Indole compounds which are useful as estrogenic agents, as well as pharmaceutical compositions and methods of treatment utilizing these compounds.

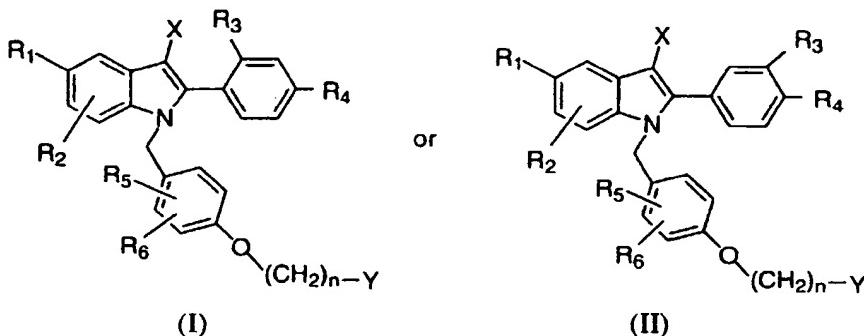
5 The use of hormone replacement therapy for bone loss prevention in post-menopausal women is well precedented. The normal protocol calls for estrogen supplementation using such formulations containing estrone, estriol, ethynodiol or conjugated estrogens isolated from natural sources (i.e. Premarin® conjugated estrogens from Wyeth-Ayerst). In some patients, therapy may be contraindicated due to the proliferative effects of unopposed estrogens (estrogens not given in combination with progestins) have on uterine tissue. This proliferation is associated with increased risk for endometriosis and/or endometrial cancer. The effects of unopposed estrogens on breast tissue is less clear, but is of some concern. The need for estrogens which can maintain the bone sparing effect while minimizing the proliferative effects in the uterus and breast is evident. Certain nonsteroidal antiestrogens have been shown to maintain bone mass in the ovariectomized rat model as well as in human clinical trials. Tamoxifen (sold as Novadex® brand tamoxifen citrate by Zeneca Pharmaceuticals, Wilmington, Delaware), for example, is a useful palliative for the treatment of breast cancer and has been demonstrated to exert an estrogen agonist-like effect on the bone, in humans. However, it is also a partial agonist in the uterus and this is cause for some concern. Raloxifene, a benzothiophene antiestrogen, has been shown to stimulate uterine growth in the ovariectomized rat to a lesser extent than Tamoxifen while maintaining the ability to spare bone. A suitable review of tissue selective estrogens is seen in the article "Tissue-Selective Actions Of Estrogen Analogs", *Bone* Vol. 17, No. 4, October 1995, 181S-190S.

10 20 The use of indoles as estrogen antagonists has been reported by Von Angerer, Chemical Abstracts, Vol. 99, No. 7 (1983), Abstract No. 53886u. Also, see, J.Med.Chem. 1990, 33, 2635-2640; J.Med.Chem. 1987, 30, 131-136. Also see Ger. Offen., DE 3821148 A1 891228 and WO 96/03375. These prior art compounds share some structural similarities with the present compounds, but are functionally different. For compounds containing a basic amine, there is no phenyl group to rigidify the side chain. The reported data for these compounds indicates that they may have a weaker binding 25 to estrogen receptor than the compounds of the present invention and the reported compounds containing the basic side chain show some uterotrophic effect in the rat uterus. One compound from the listed family of compounds in WO 96/03375 possesses a benzyl group, but does not have a basic side chain. The majority of these compounds fall into a class of compounds best characterized as being "pure antiestrogens". Many of the compounds described presently, 30 due to their particular side chain, act as pure antiestrogens in the uterus, however, show strong estrogenic action in the bone and cardiovascular systems. No such action is demonstrated for the related prior art compounds described herein.

35 45 WO A 95 17383 (Kar Bio AB) describes indole antiestrogens with long straight chains. Another related patent WO A 93 10741 describes 5-Hydroxyindole with a generic descriptor incorporating other side chains. WO 93/23374 (Otsuka Pharmaceuticals, Japan) describes compounds which differ from the present invention; where R₃ in the present formulas I and II, below, is defined as thioalkyl and the reference discloses no such compounds having chains from the indole nitrogen having the same structure as the ones provided by the present invention. Where the side chain claimed is similar to that described herein, the compounds are amides: Acylated indoles are not claimed in the present invention.

2-Phenylindoles of the general structure type shown in formulas (I) and (II) are estrogen agonists/antagonists useful for the treatment of diseases associated with estrogen deficiency. The compounds of the present invention show 40 strong binding to the estrogen receptor. *In vitro* assays, including an Ishikawa alkaline phosphatase assay and an ERE transfection assay, show these compounds are antiestrogens with little to no intrinsic estrogenicity and they have proven capable of completely antagonizing the effects of 17 β -estradiol while showing little or no uterine stimulation in a rat uterine assay when dosed alone. Additionally, some of these compounds are capable of inhibiting bone loss in an ovariectomized rat while showing little or no uterine stimulation. These compounds also decrease the weight gain normally seen in the ovariectomized animals as well as reduce total cholesterol levels.

50 The present invention includes compounds of the formulas I or II, below:



wherein:

R_1 is selected from H, OH or the C₁-C₁₂ esters (straight chain or branched) or C₁-C₁₂ (straight chain or branched or cyclic) alkyl ethers thereof, or halogens; or C₁-C₄ halogenated ethers including trifluoromethyl ether and trichloromethyl ether.

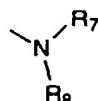
R_2 , R_3 , R_4 , R_5 , and R_6 are independently selected from H, OH or the C_1 - C_{12} esters (straight chain or branched) or C_1 - C_{12} alkyl ethers (straight chain or branched or cyclic) thereof, halogens, or C_1 - C_4 halogenated ethers including trifluoromethyl ether and trichloromethyl ether, cyano, C_1 - C_6 alkyl (straight chain or branched), or trifluoromethyl, with the proviso that, when R_1 is H, R_2 is not OH.

X is selected from H, C₁-C₆ alkyl, cyano, nitro, trifluoromethyl, halogen;

n is 2 or 3.

Y is selected from:

a) the moiety:



wherein R₇ and R₈ are independently selected from the group of H, C₁-C₆ alkyl, or phenyl optionally substituted by CN, C₁-C₆ alkyl (straight chain or branched), C₁-C₆ alkoxy (straight chain or branched), halogen, -OH, -CF₃, or -OCF₃;

b) a five-membered saturated, unsaturated or partially unsaturated heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NH-, -N(C₁C₄ alkyl)-, -N=, and -S(O)_m-, wherein m is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ acyloxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, -CO₂H-, -CN-, -CONHR₁-, -NH₂-, C₁-C₄ alkylamino, di(C₁-C₄)alkylamino, -NHSO₂R₁-, -NHCOR₁-, -NO₂, and phenyl optionally substituted with 1-3 (C₁-C₄)alkyl;

c) a six-membered saturated, unsaturated or partially unsaturated heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NH-, -N(C₁C₄ alkyl)-, -N=, and -S(O)_m-, wherein m is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ acyloxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, -CO₂H-, -CN-, -CONHR₁-, -NH₂-, C₁-C₄ alkylamino, di(C₁-C₄)alkylamino, -NHSO₂R₁-, -NHCOR₁-, -NO₂, and phenyl optionally substituted with 1-3 (C₁-C₄)alkyl;

d) a seven-membered saturated, unsaturated or partially unsaturated heterocycle containing up to two heteroatoms selected from the group consisting of $-O-$, $-NH-$, $-N(C_1C_4\text{ alkyl})-$, $-N=$, and $-S(O)_m-$, wherein m is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C_1-C_4 alkyl, trihalomethyl, C_1-C_4 alkoxy, trihalomethoxy, C_1-C_4 acyloxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, hydroxy (C_1-C_4)alkyl, $-CO_2H-$, $-CN-$, $-CONHR_1-$, $-NH_2-$, C_1-C_4 alkylamino, di(C_1-C_4)alkylamino, $-NHSO_2R_1-$, $-NHCOR_1-$, $-NO_2$, and phenyl optionally substituted with

1-3 (C_1-C_4)alkyl; or

5 e) a bicyclic heterocycle containing from 6-12 carbon atoms either bridged or fused and containing up to two heteroatoms selected from the group consisting of -O-, -NH-, -N(C_1C_4 alkyl)-, and -S(O)_m-, wherein m is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C_1-C_4 alkyl, trihalomethyl, C_1-C_4 alkoxy, trihalomethoxy, C_1-C_4 acyloxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, hydroxy (C_1-C_4)alkyl, -CO₂H-, -CN-, -CONHR₁-, -NH₂-, C_1-C_4 alkylamino, di(C_1-C_4)alkylamino, -NHSO₂R₁-, -NHCOR₁-, -NO₂, and phenyl optionally substituted with 1-3 (C_1-C_4) alkyl;

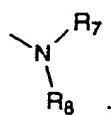
10 and the pharmaceutically acceptable salts thereof.

The more preferred compounds of this invention are those having the general structures I or II, above, wherein:

15 R_1 is selected from H, OH or the C_1-C_{12} esters or alkyl ethers thereof, halogen;

R_2 , R_3 , R_4 , R_5 , and R_6 are independently selected from H, OH or the C_1-C_{12} esters or alkyl ethers thereof, halogen, cyano, C_1-C_6 alkyl, or trihalomethyl, preferably trifluoromethyl, with the proviso that, when R_1 is H, R_2 is not OH; X is selected from H, C_1-C_6 alkyl, cyano, nitro, trifluoromethyl, halogen;

Y is the moiety

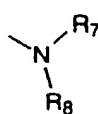


25 R_7 and R_8 are selected independently from H, C_1-C_6 alkyl, or combined by -(CH₂)_p-, wherein p is an integer of from 2 to 6, so as to form a ring, the ring being optionally substituted by up to three substituents selected from the group of hydrogen, hydroxyl, halo, C_1-C_4 alkyl, trihalomethyl, C_1-C_4 alkoxy, trihalomethoxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, hydroxy (C_1-C_4)alkyl, -CO₂H-, -CN, -CONH(C_1-C_4), -NH₃, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, -NHSO₂(C_1-C_4), -NHCO(C_1-C_4), and -NO₂;

30 and the pharmaceutically acceptable salts thereof.

The rings formed by a concatenated R_7 and R_8 , mentioned above, may include, but are not limited to, aziridine, azetidine, pyrrolidine, piperidine, hexamethyleneamine or heptamethyleneamine rings.

35 The most preferred compounds of the present invention are those having the structural formulas I or II, above, wherein R_1 is OH; R_2 - R_6 are as defined above; X is selected from the group of Cl, NO₂, CN, CF₃, or CH₃; and Y is the moiety



45 and R_7 and R_8 are concatenated together as -(CH₂)_r-, wherein r is an integer of from 4 to 6, to form a ring optionally substituted by up to three substituents selected from the group of hydrogen, hydroxyl, halo, C_1-C_4 alkyl, trihalomethyl, C_1-C_4 alkoxy, trihalomethoxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, hydroxy (C_1-C_4)alkyl, -CO₂H-, -CN, -CONH(C_1-C_4)alkyl, -NH₂, C_1-C_4 alkylamino, di(C_1-C_4)alkylamino, -NHSO₂(C_1-C_4)alkyl, -NHCO(C_1-C_4)alkyl, and -NO₂;

50 and the pharmaceutically acceptable salts thereof.

In another embodiment of this invention, when R_7 and R_8 are concatenated together as -(CH₂)_p-, wherein p is an integer of from 2 to 6, preferably 4 to 6, the ring so formed is optionally substituted with 1-3 substituents selected from a group containing C_1-C_3 alkyl, trifluoromethyl, halogen, hydrogen, phenyl, nitro, -CN.

55 The invention includes sulfate, sulfonates and sulfate esters of phenolic groups. Sulfates can be readily prepared by the reaction of the free phenolic compounds with sulfur trioxide complexed with an amine such as pyridine, trimethylamine, triethylamine, etc. Sulfonates can be prepared by treating the free phenolic compound with the desired amino or alkylamino or dialkylamino sulfamyl chloride in the presence of a suitable base such as pyridine. Sulfate esters can be prepared by reaction of the free phenol with the desired alkanesulfonyl chloride in the presence of a suitable base

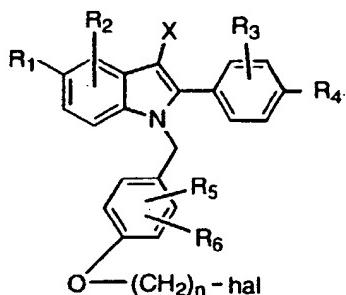
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such as pyridine. Additionally, this invention includes compounds containing phosphates at the phenol as well as dialkyl phosphates. Phosphates can be prepared by reaction of the phenol with the appropriate chlorophosphate. The dialkyl phosphates can be hydrolyzed to yield the free phosphates. Phosphinates are also claimed where the phenol is reacted with the desired dialkylphosphinic chloride to yield the desired dialkylphosphinate of the phenol.

The invention includes acceptable salt forms formed from the addition reaction with either inorganic or organic acids. Inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, nitric acid useful as well as organic acids such as acetic acid, propionic acid, citric acid, maleic acid, malic acid, tartaric acid, phthalic acid, succinic acid, methanesulfonic acid, toluenesulfonic acid, naphthalenesulfonic acid, camphorsulfonic acid, benzenesulfonic acid are useful. It is known that compounds possessing a basic nitrogen can be complexed with many different acids (both protic and non-protic) and usually it is preferred to administer a compound of this invention in the form of an acid addition salt. Additionally, this invention includes quaternary ammonium salts of the compounds herein. These can be prepared by reacting the nucleophilic amines of the side chain with a suitably reactive alkylating agent such as an alkyl halide or benzyl halide.

This invention provides processes for preparing the compounds of formula I or II which comprise one of the following:

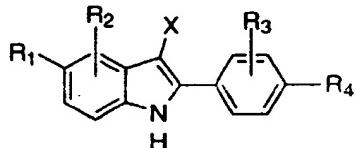
a) reacting a compound of formula



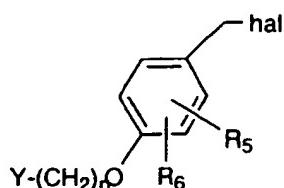
wherein n, R₁-R₆ and X are as defined above and hal is chlorine or bromine with a compound of formula:



where R₇ and R₈ are as defined above to give a corresponding compound of formula I or II; or
b) reacting a compound of formula



wherein R₁-R₄ and X are as defined above in the presence of a base, e.g NaH, with a compound of formula



wherein n, R₅, R₆ and Y are as defined above and hal is a halogen, e.g Cl or Br to give a corresponding compound of Formula I;

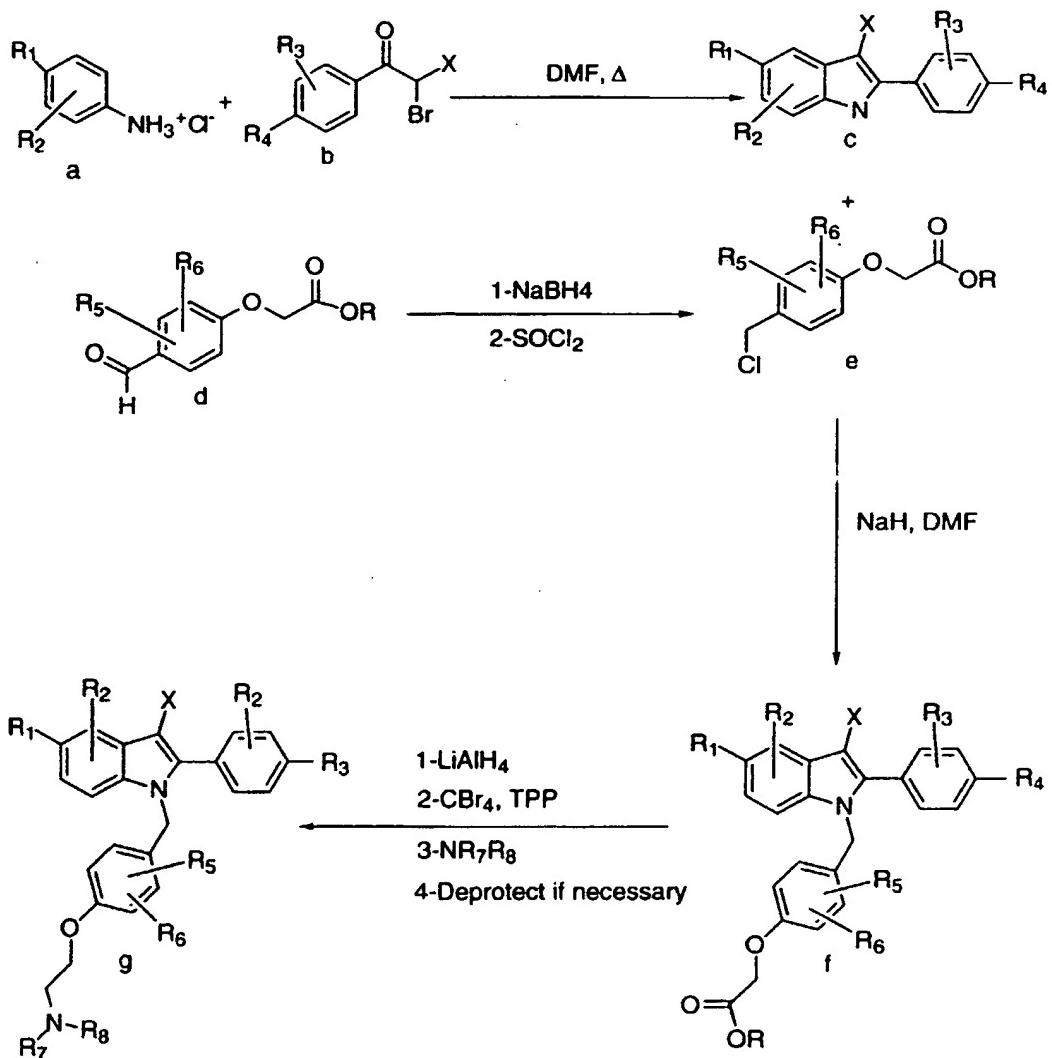
if necessary protecting any reactive substituent groups during each process above and removing same; and

if desired converting a phenolic group present to a phosphate, sulfate, sulfamate or sulfate ester; and further if desired converting the compound of formula I or II to a pharmaceutically acceptable salt.

Methods

Compounds of this invention can be synthesized in a general sense according to Scherme 1, below.

Scheme 1



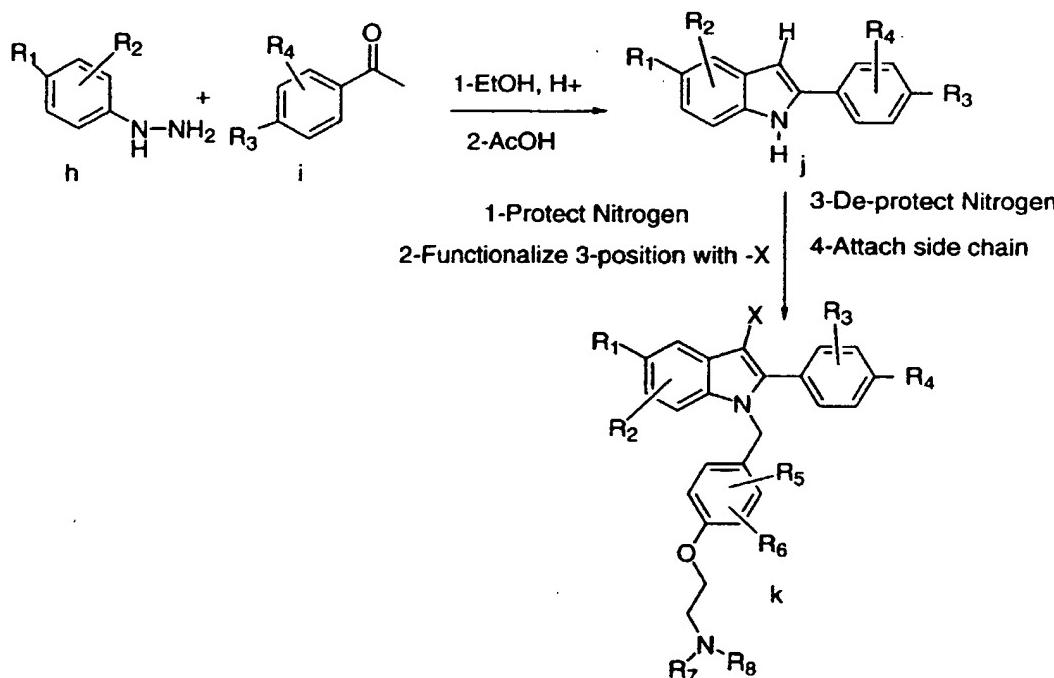
The initial indole synthesis is accomplished by heating an appropriately substituted alpha-bromo ketone (b) with the desired aniline (a) in DMF to form the indole (c). The product is then alkylated with a benzyl chloride (e) to give the substituted indole (f). The benzyl chloride (e) can be readily prepared from the aldehyde (d) in 2 steps as given. Product

(g) can be prepared from (f) by reduction of the ester, conversion of the alcohol to a bromide, displacement of the bromide with the desired amine in a suitable solvent such as THF or DMF, and finally, deprotection if necessary. Deprotection is necessary when either R₁ or R₂ or both is a protected phenol. The preferred protecting group is a benzyl group which can be conveniently removed by several conventional methods, especially hydrogenolysis.

For the synthesis of compounds with X=H, halogen, trifluoromethyl, cyano, nitro, an alternative synthesis shown in scheme 2 may be preferable. The formation of halogens at the 3-position can be easily performed with such reagents as N-chlorosuccinamide, N-bromosuccinamide, or N-iodosuccinamide. A 3-iodoindole compound obtained can be used as a precursor to the 3-trifluoromethyl compound by a coupling reaction utilizing a palladium catalyst and bis(trifluoromethyl) mercury (II). A compound with a cyano group in the 3-position can be prepared by electrophilic cyanation or alternatively the 3-position can be formylated (with a formyl iminium salt, for example) then the formyl group converted to an oxime and subsequently dehydrated to a nitrile. Alternatively, the 3-cyano compound can be synthesized by reaction of the 3-unsubstituted indole with chlorosulfonylisocyanate followed by triethylamine. A compound with the nitro group in the 3-position can be prepared by treating the indole with sodium nitrite and acetic acid. One skilled in the art recognizes these routes are not limiting and other routes are also available.

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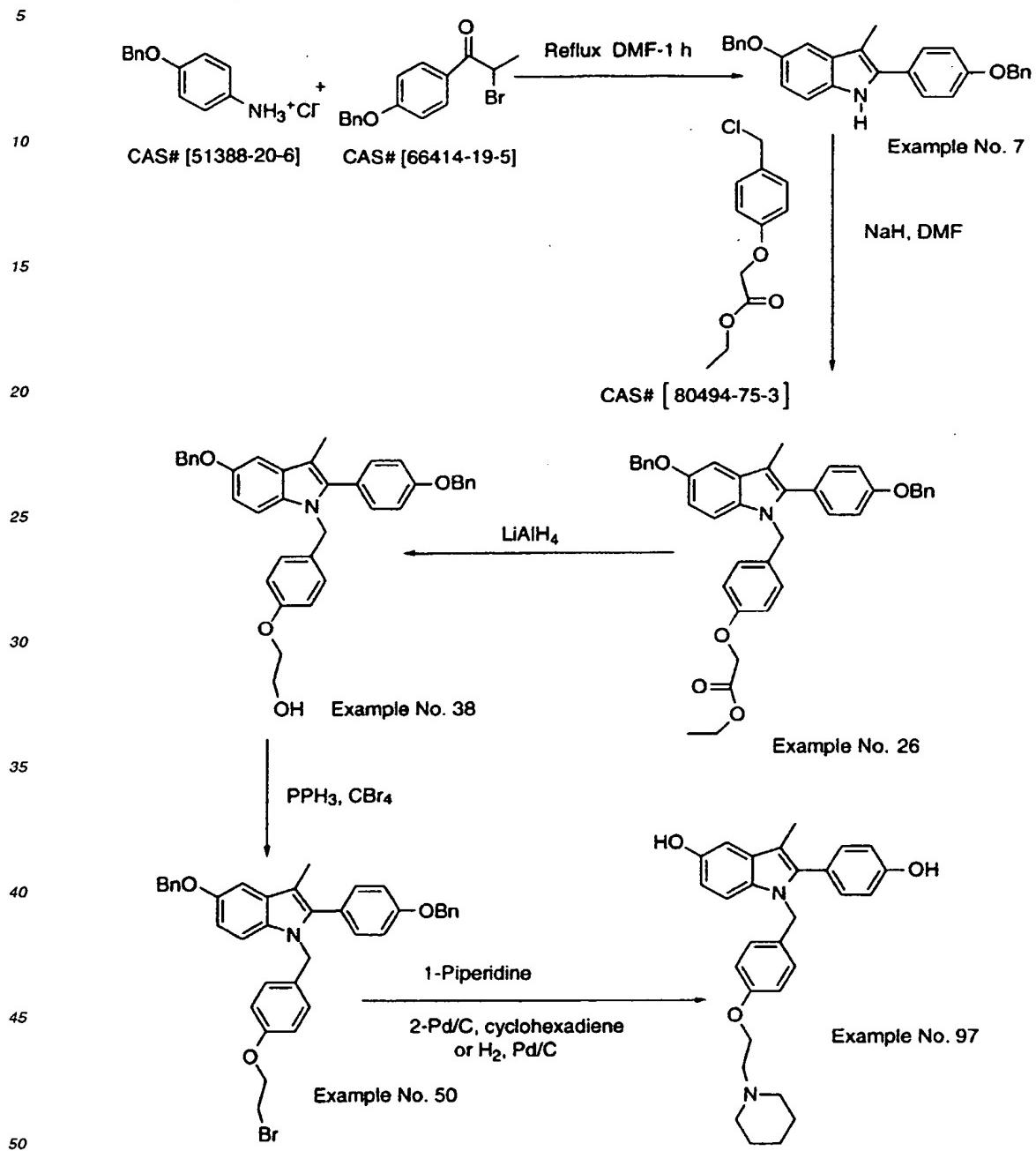
Scheme 2



Synthesis of selected representative examples are given in the following schemes:

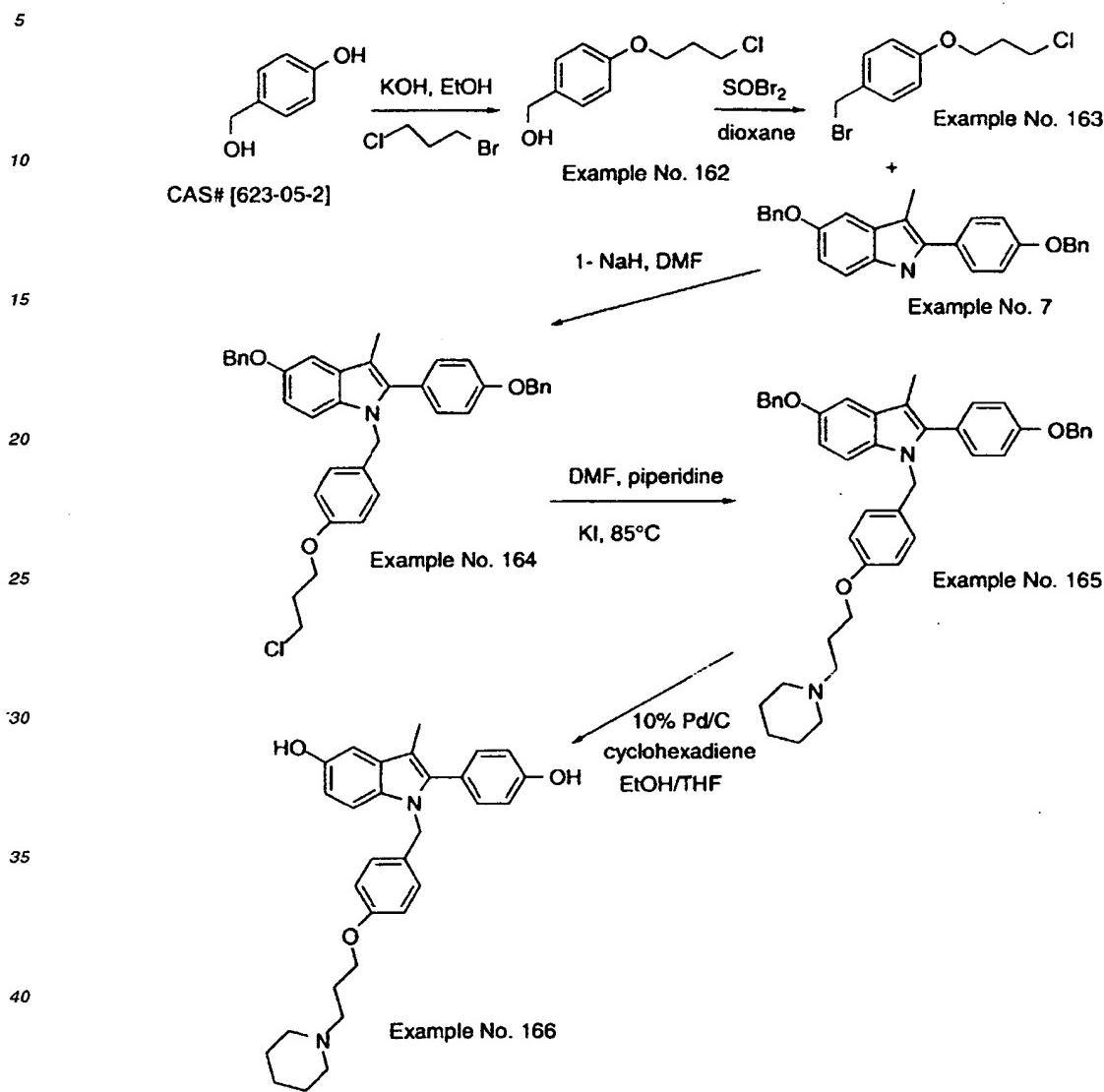
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Scheme 3

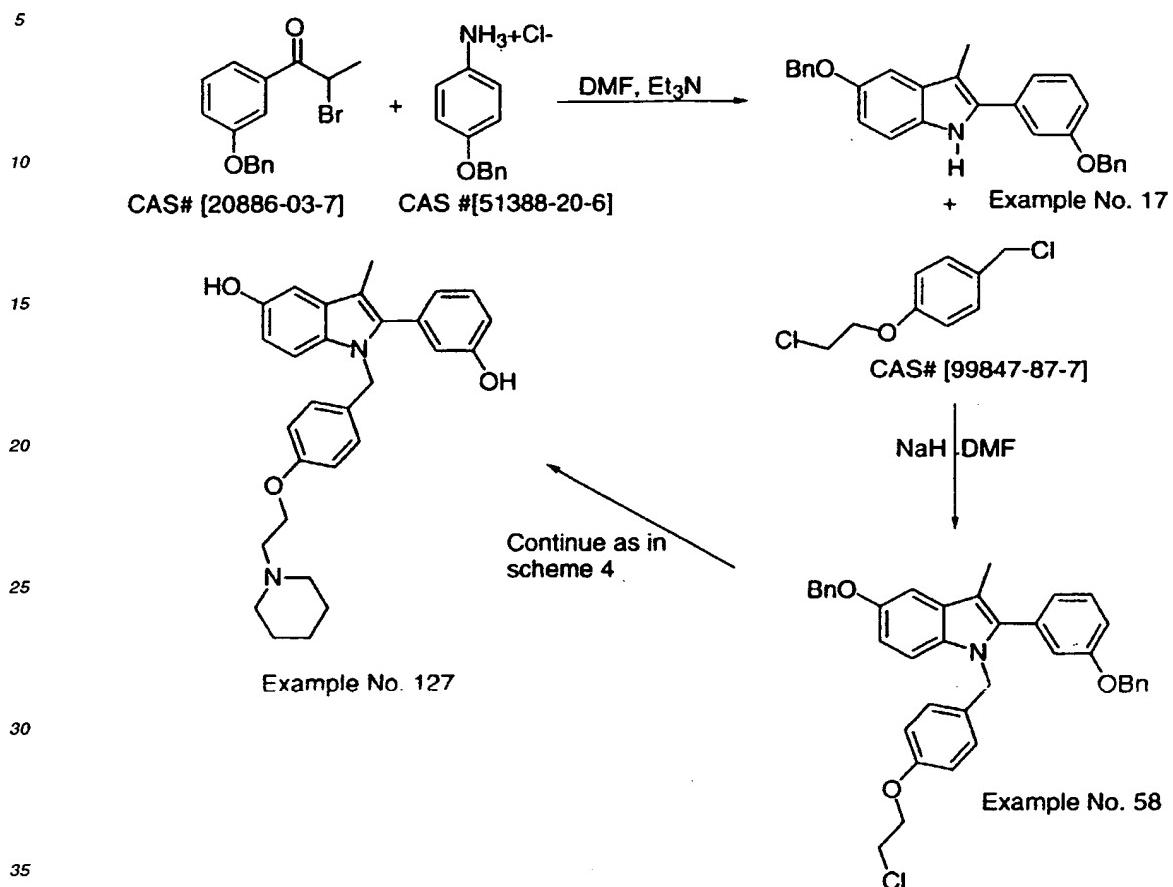
The synthesis of analogues with a 3-carbon chain (example No. 166) between the oxygen and the basic amine can be accomplished as shown in scheme 4.

Scheme 4



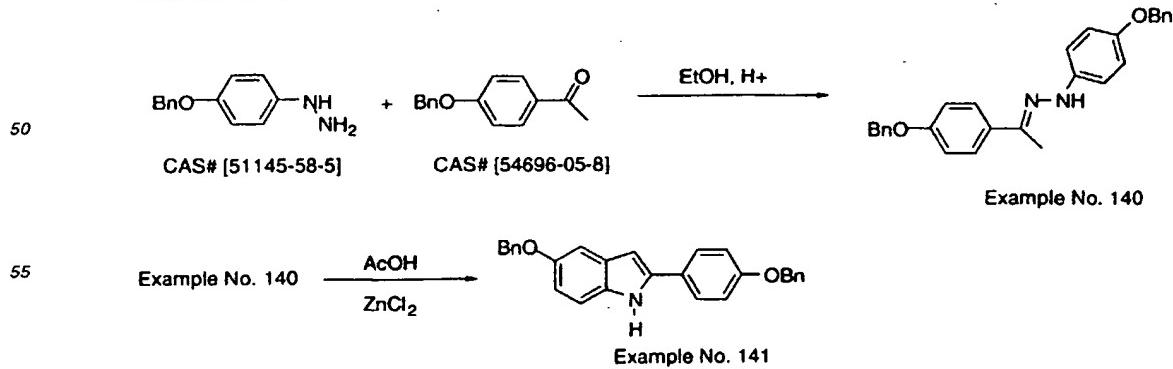
The synthetic procedure shown in scheme 4 may be used for compounds with two carbon chains analogous to example No. 97 in scheme 3. This is shown in scheme 4a for the synthesis of example No. 127.

Scheme 4a



The synthesis of indoles with alternative substituents (CN, Cl) at the 3-position of the indole both utilize the 3-unsubstituted indole No. 141 for a precursor. The indole is synthesized by the Fisher method utilizing the hydrazone derived from the condensation of 4-benzyloxyacetophenone CAS No. [54696-05-8] and 4-benzyloxyphenylhydrazine CAS No. [51145-58-5]. The hydrazone No. 140 is then cyclized in acetic acid using zinc chloride to afford the desired indole No. 141. This synthesis can be seen in scheme 5.

45 Scheme 5

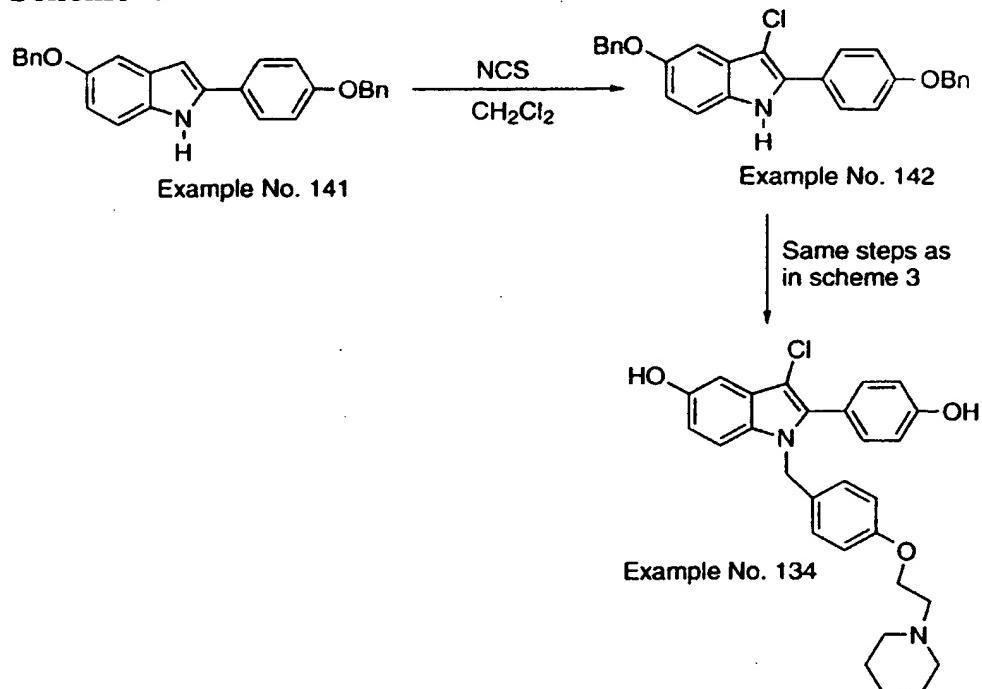


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The synthesis of 3-Chloroindole compounds is demonstrated for example No. 134 and shown, *infra*, in scheme 6. The indole No. 141 from scheme 5 is chlorinated with N-chlorosuccinamide. The 3-Chloroindole No. 142, thus obtained is taken to the final product in analogous fashion to that shown in scheme 3.

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Scheme 6



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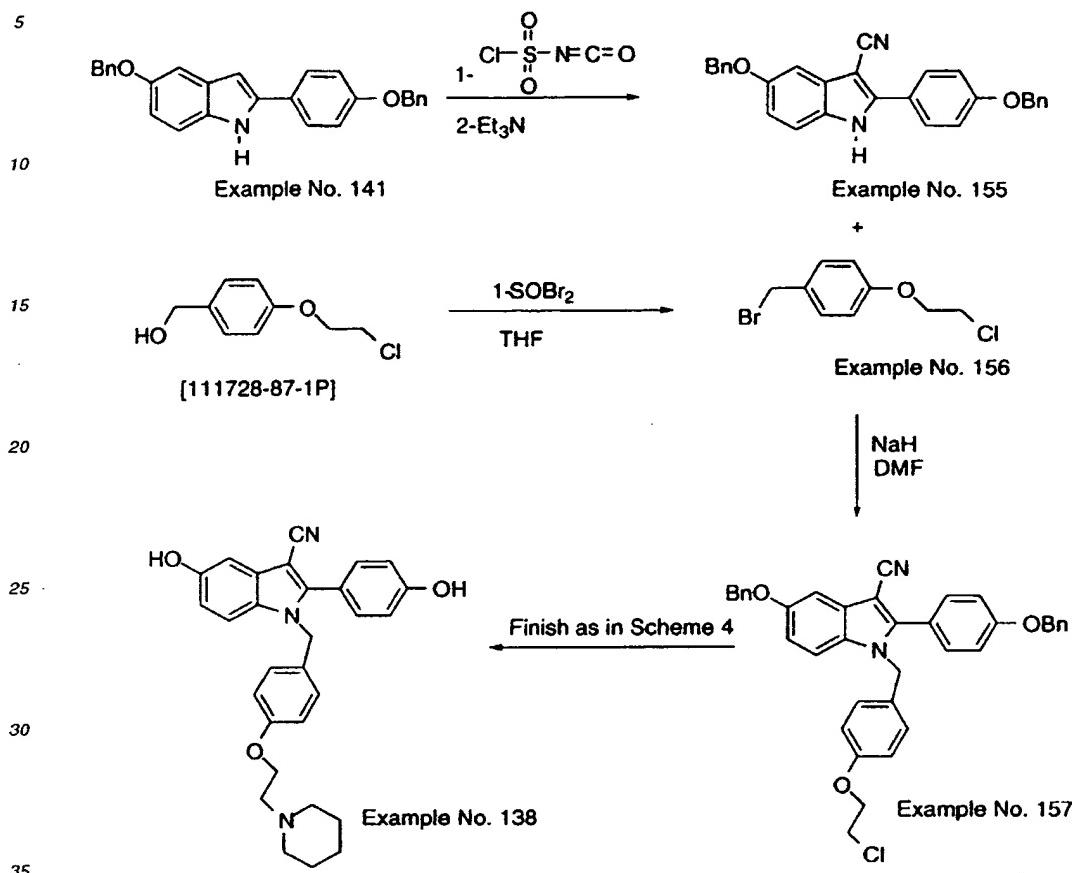
35 3-Cyano analogues are synthesized from the precursor indole No. 141 as shown in Scheme 7. Reaction of the precursor indole No. 141 with chlorosulfonyl isocyanate followed by addition of triethylamine yields the 3-Cyanoindole No. 155. The side chain is made by conversion of the benzylic alcohol of CAS No. [111728-87-1] to the benzylic bromide No. 156 using thionyl bromide in THF. The indole is alkylated by the side chain in DMF using sodium hydride to give the intermediate No. 157. This can then be taken to the final product No. 138 in an analogous fashion to that shown in scheme 4.

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Scheme 7

The compounds of the invention are selective estrogen agonists and display high affinity for the estrogen receptor. Unlike many estrogens, however, many of these compounds do not cause increases in uterine wet weight. These compounds are antiestrogenic in the uterus and can completely antagonize the trophic effects of estrogen agonists in uterine tissue. Due to the tissue selective nature of these compounds, they are useful in treating or preventing in a mammal disease states or syndromes which are caused or associated with an estrogen deficiency (in certain tissues such as bone or cardiovascular) or an excess of estrogen (in the uterus or mammary glands). They may also be used in methods of treatment for diseases or disorders which result from proliferation or abnormal development, actions or growth of endometrial or endometrial-like tissues.

The present compounds have the ability to behave like estrogen agonists by lowering cholesterol and preventing bone loss. These compounds are useful for treating many maladies which result from estrogen effects and estrogen excess or deficiency including osteoporosis, prostatic hypertrophy, male pattern baldness, vaginal and skin atrophy, acne, dysfunctional uterine bleeding, endometrial polyps, benign breast disease, uterine leiomyomas, adenomyosis, ovarian cancer, infertility, breast cancer, endometriosis, endometrial cancer, polycystic ovary syndrome, cardiovascular disease, contraception, Alzheimer's disease, cognitive decline and other CNS disorders, as well as certain cancers including melanoma, prostate cancer, cancers of the colon, CNS cancers, among others. Additionally, these compounds can be used for contraception in pre-menopausal women, as well as hormone replacement therapy in post-menopausal women or in other estrogen deficiency states where estrogen supplementation would be beneficial. They may also be used in disease states where amenorrhea is advantageous, such as leukemia, endometrial ablations, chronic renal or hepatic disease or coagulation diseases or disorders.

The compounds of this invention may also be used in methods of treatment for and prevention of bone loss, which may result from an imbalance in a individual's formation of new bone tissues and the resorption of older tissues, leading to a net loss of bone. Such bone depletion results in a range of individuals, particularly in post-menopausal women,

women who have undergone bilateral oophorectomy, those receiving or who have received extended corticosteroid therapies, those experiencing gonadal dysgenesis, and those suffering from Cushing's syndrome. Special needs for bone, including teeth and oral bone, replacement can also be addressed using these compounds in individuals with bone fractures, defective bone structures, and those receiving bone-related surgeries and/or the implantation of prosthesis.

In addition to those problems described above, these compounds can be used in treatments for osteoarthritis, hypocalcemia, hypercalcemia, Paget's disease, osteomalacia, osteohalisteresis, multiple myeloma and other forms of cancer having deleterious effects on bone tissues. Methods of treating the maladies listed herein are understood to comprise administering to an individual in need of such treatment a pharmaceutically effective amount of one or more of the compounds of this invention or a pharmaceutically acceptable salt thereof. This invention also includes pharmaceutical compositions utilizing one or more of the present compounds, and/or the pharmaceutically acceptable salts thereof, along with one or more pharmaceutically acceptable carriers, excipients, etc.

It is understood that the dosage, regimen and mode of administration of these compounds will vary according to the malady and the individual being treated and will be subject to the judgement of the medical practitioner involved. It is preferred that the administration of one or more of the compounds herein begin at a low dose and be increased until the desired effects are achieved.

Effective administration of these compounds may be given at a dose of from about 0.1 mg/day to about 1,000 mg/day. Preferably, administration will be from about 10 mg/day to about 600 mg/day, more preferably from about 50 mg/day to about 600 mg/day, in a single dose or in two or more divided doses. Such doses may be administered in any manner useful in directing the active compounds herein to the recipient's bloodstream, including orally, via implants, parenterally (including intravenous, intraperitoneal and subcutaneous injections), rectally, vaginally, and transdermally. For the purposes of this disclosure, transdermal administrations are understood to include all administrations across the surface of the body and the inner linings of bodily passages including epithelial and mucosal tissues. Such administrations may be carried out using the present compounds, or pharmaceutically acceptable salts thereof, in lotions, creams, foams, patches, suspensions, solutions, and suppositories (rectal and vaginal).

Oral formulations containing the active compounds of this invention may comprise any conventionally used oral forms, including tablets, capsules, buccal forms, troches, lozenges and oral liquids, suspensions or solutions. Capsules may contain mixtures of the active compound(s) with inert fillers and/or diluents such as the pharmaceutically acceptable starches (e.g. corn, potato or tapioca starch), sugars, artificial sweetening agents, powdered celluloses, such as crystalline and microcrystalline celluloses, flours, gelatins, gums, etc. Useful tablet formulations may be made by conventional compression, wet granulation or dry granulation methods and utilize pharmaceutically acceptable diluents, binding agents, lubricants, disintegrants, suspending or stabilizing agents, including, but not limited to, magnesium stearate, stearic acid, talc, sodium lauryl sulfate, microcrystalline cellulose, carboxymethylcellulose calcium, polyvinylpyrrolidone, gelatin, alginic acid, acacia gum, xanthan gum, sodium citrate, complex silicates, calcium carbonate, glycine, dextrin, sucrose, sorbitol, dicalcium phosphate, calcium sulfate, lactose, kaolin, mannitol, sodium chloride, talc, dry starches and powdered sugar. Oral formulations herein may utilize standard delay or time release formulations to alter the absorption of the active compound(s). Suppository formulations may be made from traditional materials, including cocoa butter, with or without the addition of waxes to alter the suppository's melting point, and glycerin. Water soluble suppository bases, such as polyethylene glycols of various molecular weights, may also be used.

Aldrich Sure Seal™ Solvents, anhydrous without further purification, may be used for the reactions described herein and may be obtained from Aldrich Chemical Company. All reactions were carried out under a nitrogen atmosphere. Chromatography was performed using 230-400 mesh silica gel (Merck Grade 60, Aldrich Chemical Company). Thin layer chromatography was performed with Silica Gel 60 F254 plates from EM Science. ¹H NMR spectra were obtained on a Bruker AM-400 or Bruker DPX-300 instrument in DMSO and chemical shifts reported in ppm. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer diffraction grating or Perkin-Elmer 784 spectrophotometers. Mass spectra were recorded on a Kratos MS 50 or Finnigan 8230 mass spectrometers. Elemental analyses were obtained with a Perkin-Elmer 2400 elemental analyzer. Compounds for which CHN are reported are within 0.4% of the theoretical value for the formula given unless expressed otherwise. Compound nomenclature was generally arrived at by use of the Beilstein Autonom™ program.

50 Synthesis of α -bromo ketones

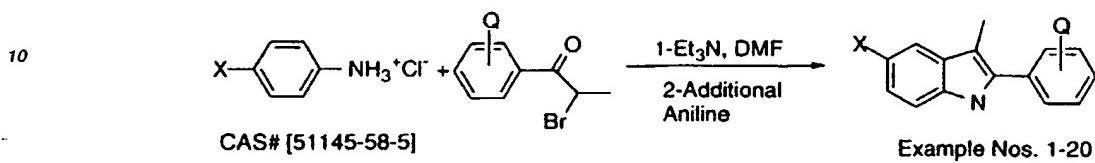
Method a

The synthesis of the alpha bromo ketones is conveniently accomplished by simply dissolving the starting phenyl ketone in ethyl ether (0.05-0.10 M) and at room temperature, 1.1 equivalents of bromine is added in dropwise. The reaction can be monitored by TLC for consumption of starting materials. The reaction is worked up by washing with an aqueous sodium bicarbonate solution followed by a 10% aqueous sodium sulfite solution. The ether layer is washed with brine and dried over magnesium sulfate. Concentration of the reaction mixture typically yields the bromoketones

in good yield and purity. The bromoketones were taken "as is" (without purification or characterization) to the next step.

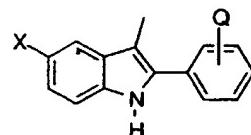
5 3-Methyl indoles

Scheme 8



15

20



25

Table 1

30

No. 1	H	H
No. 1a	F	OBn
No. 2	H	4'-OBn

35

40

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50

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Table 1 (Cont'd)

No.	Structure	Label
No. 3	OBn	H
No. 4	OBn	4'-OMe
No. 5	OMe	4'-OMe
No. 6	OBn	4'-OEt
No. 7	OBn	4'-OBn
No. 8	OBn	4'-F
No. 9	OBn	3'-OMe,4'-OBn
No. 10	OBn	3',4'-OCH ₂ O-
No. 11	OBn	4'-O-iPr
No. 12	OBn	4'-O-Cp
No. 13	OBn	4'-CF ₃
No. 14	OBn	4'-CH ₃
No. 15	OBn	4'-Cl
No. 16	OBn	2'-OMe,4'-OMe
No. 17	OBn	3'-OBn
No. 18	OBn	4'-OBn,3'-F
No. 19	OBn	3'-OMe
No. 20	OBn	4'-OCF ₃

Method 1Illustrated For Example No. 75-Benzylxy-2-(4-benzylxy-phenyl)-3-methyl-1H-indole

A flask was charged with 4-benzylxyaniline hydrochloride CAS No. [51145-58-5], (45 g, 0.23 mol), 4'-benzylxy-2-bromophenylpropiophenone CAS No. [66414-19-5] (21g, 0.066 mol), and 50 mL DMF. The reaction was heated at reflux for 30 minutes and then cooled to rt and then partitioned between 250 mL EtOAc and 100 mL 1N HCl (aq). The EtOAc was washed with NaHCO₃ (aq) and brine, then dried over MgSO₄. The solution was concentrated and the residue taken up in CH₂Cl₂ and hexanes added to precipitate out 25g of a crude solid. The solid was dissolved in CH₂Cl₂ and evaporated onto silica gel and chromatographed using CH₂Cl₂/Hexane (1:5) to yield 9.2 g of a tan solid (33%); Mp = 150-152°C; ¹H NMR (DMSO) 10.88 (s, 1 H), 7.56 (d, 2 H, J = 8.8 Hz), 7.48 (d, 4 H, J = 7.9 Hz), 7.42-7.29 (m, 6 H), 7.21 (d, 1 H, J = 7.0 Hz), 7.13 (d, 2 H, J = 8.8 Hz), 7.08 (d, 1 H, J = 2.2 Hz), 6.94 (dd, 1 H, J = 8.8, 2.4 Hz), 5.16 (s, 2 H), 5.11 (s, 2 H), 2.33 (s, 3 H); IR (KBr) 3470, 2880, 2820, 1620 cm⁻¹; MS el m/z 419.

Method 2 (shown in scheme 8)Also Illustrated For Example No. 7

Reagents used were same as in method 1 except the additional use of triethylamine in this method. The bromoke-

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tone CAS No. [66414-19-5] (50.0 g, 0.16 mol) in 200 mL DMF was treated with the aniline hydrochloride CAS No. [51145-58-5] (44 g, 0.22 mol) and the reaction purged with nitrogen for about 10 minutes. The triethylamine (54.6 mL) was added and the reaction was heated at 120°C for 2 hours. TLC analysis (EtOAc/hexanes) shows the starting material has disappeared forming a more polar spot. The reaction mixture is allowed to cool down and an additional 5 48 g of the aniline hydrochloride was added. The reaction was heated to 150°C for 2 hours. An additional 5 grams of the aniline hydrochloride was added and the reaction was heated at 150°C for an additional 30 minutes. The reaction mixture is allowed to cool to room temperature and then poured into approximately 1.5 liters of water and extracted with 2 liters of ethyl acetate. Solids are dissolved with additional ethyl acetate as necessary. The ethyl acetate layer is washed with 1 liter of 1 N NaOH solution aq., 1 liter of water, brine, then dried over magnesium sulfate and filtered. 10 The organic layers were concentrated down to yield a crude solid which is stirred with 500 mL of methanol and filtered. This solid is then stirred with 500 mL of ethyl ether and filtered. The solid is stirred alternatively with methanol and ether until it is of whitish color and has a melting point similar to that described for No. 7 in method 1. Reaction yields 36 grams of product.

15 **Physical Data for Indoles**

The following 3-methyl indoles (No. 1- No. 20) were synthesized according to the procedure outlined in scheme 2 using method 2 using the appropriately substituted bromoketones (prepared as given above) and anilines (commercially available; Aldrich) as starting materials.

20 **Example No. 1 2-Phenyl-3-methyl-1H-indole**

Mp = 90 -94°C; ¹H NMR (DMSO) 11.13 (s, 1 H), 7.68 - 7.64 (m, 2 H), 7.54 - 7.46 (m, 3 H), 7.37 - 7.32 (m, 2 H), 7.12 - 7.06 (m, 1 H), 7.03 - 6.97 (m, 1 H), 2.40 (s, 3 H); MS el m/z 207 (M+).

25 **Example No. 1a 5-Fluoro-2-(4-benzylxy-phenyl)-3-methyl-1H-indole**

Mp = 143 - 146°C.

30 **Example No. 2 2-(4-Benzylxy-phenyl)-3-methyl-1H-indole**

Mp = 118 -120°C; ¹H NMR (DMSO) 11.03 (s, 1 H), 7.57 (dd, 2 H, J = 2.0 Hz, 6.6 Hz), 7.48 - 7.46 (m, 3 H), 7.44 - 7.28 (m, 4 H), 7.18 - 7.11 (m, 2 H), 7.08 - 7.03 (m, 1 H), 7.0 - 6.95 (m, 1 H), 5.16 (s, 2 H), 2.36 (s, 3 H); MS el m/z 313 (M+).

35 **Example No. 3 5-Benzylxy-2-phenyl-3-methyl-1H-indole**

Mp = 141-144°C; ¹H NMR(DMSO) 10.98 (s, 1 H), 7.65-7.61 (m, 2 H), 7.51-7.44 (m, 4 H), 7.42-7.28 (m, 4 H), 7.23 (d, 1 H, J = 8.8Hz), 7.10 (d, 1 H, J = 2.5Hz), 6.80 (d, 1 H , J = 6.0Hz), 5.10 (s, 2 H), 2.36 (s, 3 H); MS el m/z 313 (M+).

40 **Example No. 4 5-Benzylxy-2-(4-methoxy-phenyl)-3-methyl-1H-indole**

Mp =158°C; ¹H NMR 10.85 (brs, 1 H), 7.56 (d, 2 H, J = 8.8 Hz), 7.48 (d, 2 H, J = 8.3 Hz), 7.45 - 7.36 (m, 2 H), 7.34 -7.28 (m, 1 H), 7.21 (d, 1 H, J = 8.6 Hz), 7.09 - 7.04 (m, 3 H), 6.79 (dd, 1 H, J = 8.8 Hz), 5.11 (s, 2 H), 3.80 (s, 3 H), 2.33 (s, 3 H); IR (KBr) 3400, 2900, 1610 cm⁻¹; MS el m/z 343 (M+); CHN calcd for C₂₃H₂₁NO₂ + 0.25 H₂O.

45 **Example No. 5 5-methoxy-2-(4-methoxy-phenyl)-3-methyl-1H-Indole**

Mp = 139 - 142°C; ¹H NMR (DMSO) 10.85 (s , 1 H), 7.57 (d , 2 H , J = 8.8 Hz), 7.19 (d , 1 H , J = 8.6 Hz), 7.04 (d, 2 H, J = 6.8 Hz), 6.95 (d , 1H , J = 2.2 Hz), 6.71 (dd , 1H , J = 8.5 Hz, J = 2.4 Hz), 3.80 (s , 3 H), 3.76 (s , 3 H), 2.33 (s , 3 H); MS el m/z 267 (M+); CHN calc for C₁₇H₁₇NO₂.

Example No. 6 5-Benzylxy-2-(4-ethoxy-phenyl)-3-methyl-1H-indole

Mp = 143-145°C; ¹H NMR (DMSO) 10.86 (s , 1 H), 7.54 (d , 2 H , J = 8.5 Hz), 7.46 (d, 2 H, J J = 7.3 Hz), 7.41-7.37 (m, 2 H), 7.32-7.30 (m, 1 H), 7.20 (d, 1 H, J = 8.6 Hz), 7.05 (d , 1 H), 7.03 (d, 2 H, J = 8.8 Hz), 6.79 (dd , 1 H, J = 8.6 Hz, J = 2.4 Hz), 5.10 (s, 2 H), 4.07 (q , 2 H, J = 6.8 Hz), 2.32 (s , 3 H), 1.34 (t , 3 H, J = 7.0 Hz); MS el m/z 357 (M+).

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Example No. 8 5-Benzylxy-2-(4-fluoro-phenyl)-3-methyl-1H-indole

5 Mp = 132°C; ¹H NMR (DMSO) 11.0 (s, 1 H), 7.68-7.64 (m, 2 H), 7.49-7.47
(m, 2 H), 7.41-7.31 (m, 5 H), 7.23 (d, 1 H, J = 8.8 Hz), 7.10 (d, 1 H, J = 2.4 Hz), 6.82 (dd, 1 H, J = 8.8, 2.4 Hz), 5.11
(s, 2 H), 2.34 (s, 3 H); MS El m/z 331; CHN calcd for C₂₂H₁₈FNO.

Example No. 9 5-Benzylxy-2-(4-benzylxy-3-methoxy-phenyl)-3-methyl-1H-indole

10 Mp = 155 -158°C ; ¹H NMR (DMSO) 10.88 (s , 1H), 7.50 - 7.45 (m , 4 H), 7.41-7.35 (m , 6H), 7.22 - 7.20 (m , 2 H),
7.14 (s , 2 H) , 7.08 (d , 1H , J = 2.2Hz), 6.78 (dd, 1H, J = 8.5 Hz, J = 2.4Hz), 5.13 (s , 2H) , 5.11(s , 2H), 3.85 (s , 3H),
2.35 (s, 3H); MS el m/z 449 (M+).

Example No. 10 2-Benzo[1,3]dioxol-5-yl-5-benzylxy-3-methyl-1H-indole

15 Mp = 142-145°C; ¹H NMR (DMSO) 10.86 (s , 1H), 7.48 (d, 2 H , J = 7.0 Hz), 7.40-7.30 (m , 3 H), 7.20 (m , 2 H),
7.10 - 7.05 (m , 3 H), 6.78 (dd, 1 H, J = 8.8 Hz, J = 2.4 Hz), 6.06 (s, 2 H), 5.10 (s , 2H), 2.31 (s , 3 H); MS el m/z 357
(M+); CHN calc for C₂₃H₁₉NO₃.

Example No. 11 5-Benzylxy-2-(4-isopropoxy-phenyl)-3-methyl-1H-indole

20 Mp = 136 - 138°C; ¹H NMR (DMSO) 10.86 (s , 1 H), 7.55 - 7.51 (m , 2 H), 7.50 - 7.47 (d, 2 H, J = 7.3 Hz), 7.40 -
7.34 (m , 2 H), 7.39 - 7.28 (m , 1 H), 7.20 (d, 1 H, J = 8.7 Hz), 7.06 (d, 1 H, J = 2.2 Hz), 7.02 (d, 2 H, J = 8.8 Hz), 6.77
(dd, 1 H, J=2.4 Hz, 8.8 Hz), 5.10 (s, 2 H), 4.68 - 4.62 (m, 1 H), 2.32 (s, 3 H), 1.28 (d, 6 H, J=6.0 Hz); MS el m/z 371 (M+).

25 **Example No. 12 5-Benzylxy-2-(4-cycloopenyloxy-phenyl)-3-methyl-1H-indole**

Mp = 161 - 167°C; ¹H NMR (DMSO) 10.85 (s , 1 H), 7.53 (d, 2 H, J = 8.8 Hz), 7.47 (d, 2 H, J = 8.4 Hz), 7.40 - 7.36
(m , 2 H), 7.33 - 7.28 (m , 1 H), 7.20 (d, 1 H, J = 8.6 Hz), 7.07 (d, 1 H, J = 2.4 Hz), 7.01 (d, 2 H, J = 8.8 Hz), 6.78 (dd,
1 H, J = 8.6 Hz, 2.2 Hz), 5.10 (s, 2 H), 4.88 - 4.84 (m, 1 H), 2.32 (s, 3 H), 1.99 - 1.88 (m, 2 H), 1.78 - 1.69 (m, 4 H),
1.64 - 1.52 (m, 2 H); IR (KBr) 3400, 2920, 1600 cm⁻¹; MS el m/z 397 (M+); CHN calcd for C₂₇H₂₇NO₂ + 0.25 H₂O.

Example No. 13 5-Benzylxy-2-(4-trifluoromethyl-phenyl)-3-methyl-1H-indole

35 ¹H NMR (DMSO) 11.0 (br s, 1 H), 7.87 - 7.82 (m, 4 H), 7.48 (d, 2 H, J = 8.8 Hz), 7.44 - 7.35 (m, 2 H), 7.34 - 7.26
(m , 2 H), 7.15 (d, 1 H, J = 2.2 Hz), 6.87 (dd, 1 H, J = 8.6 Hz, 2.4 Hz), 5.12 (s, 2 H), 2.41 (s, 3 H); CHN calcd for
C₂₃H₁₈F₃NO.

Example No. 14 5-Benzylxy-2-(4-methyl-phenyl)-3-methyl-1H-indole

40 Mp = 144 - 146°C; ¹H NMR (DMSO) 10.91 (s , 1 H), 7.56 - 7.20 (m, 10 H), 7.08 (d, 1 H, J = 2.4 Hz), 6.80 (dd, 1 H,
J = 2.4 Hz, 8.6 Hz), 5.11 (s, 2 H), 2.34 (s, 3 H), 2.34 (s, 3 H); MS el m/z 327(M+).

Example No. 15 5-Benzylxy-2-(4-chloro-phenyl)-3-methyl-1H-indole

45 Mp = 134-136°C; ¹H NMR (DMSO) 11.04 (s, 1H), 7.65 (d , 2H, J = 8.3Hz), 7.53 (d, 2 H , J = 8.5Hz), 7.47 (d, 2 H ,
J = 6.8 Hz), 7.41 - 7.37 (m , 2H), 7.31 - 7.28 (m , 1H), 7.25 (d , 1H , J = 8.5 Hz), 7.11 (d , 1 H , J = 2.4Hz), 6.82 (dd ,
1 H , J =8.8 Hz , J = 2.4 Hz), 5.11 (s , 2H), 2.35 (s , 3H); IR (KBr) 3380, 1210 cm⁻¹, Ms el m/z 347 (M+); CHN calc for
C₂₂H₁₈ClNO₂.

50 **Example No. 16 5-Benzylxy-2-(2,4-dimethoxy-phenyl)-3-methyl-1H-indole**

Oil; ¹H NMR (DMSO) 10.58 (s, 1 H), 7.50 - 7.18 (m, 7 H), 7.04 (d, 1 H, J = 2.4 Hz), 6.76 (dd, 1 H, J = 2.3 Hz, 8.6
Hz), 6.69 - 6.62 (m, 2 H), 5.11 (s, 2 H), 3.82 (s, 3 H), 3.78 (s, 3 H), 2.12 (s, 3 H).

55 **Example No. 17 5-Benzylxy-2-(3-benzylxy-phenyl)-3-methyl-1H-indole**

Mp = 83 - 86°C

Example No. 18 5-Benzylxy-2-(4-benzylxy-3-fluoro-phenyl)-3-methyl-1H-indole

Mp = 135 - 137°C; ¹H NMR (DMSO) 10.94 (s, 1 H), 7.50 - 7.31 (m, 13 H), 7.22 (d, 1 H, J = 8.6 Hz), 7.10 (d, 1 H, J = 2.2 Hz), 6.81 (dd, 1 H, J = 8.6 Hz, 2.2 Hz), 5.23 (s, 2 H), 5.11 (s, 2 H), 2.34 (s, 3 H); MS el m/z 437 (M+); CHN calcd for C₂₉H₂₄FNO₂

Example No. 19 5-Benzylxy-2-(3-methoxy-phenyl)-3-methyl-1H-indole

Mp = 107 - 109°C; ¹H NMR (DMSO) 11.00 (s, 1 H), 7.51 - 7.48 (m, 2 H), 7.43 - 7.20 (m, 7 H), 7.13 - 7.12 (d, 1 H, J = 2.1 Hz), 6.93 - 6.90 (dd, 1 H, J = 2.3 Hz, J = 5.7 Hz), 6.86 - 6.82 (dd, 1 H, J = 2.3 Hz, J = 6.3 Hz), 5.12 (s, 2 H), 3.83 (s, 3 H), 2.38 (s, 3 H); IR (KBr) 3400, 2900, 1600 cm⁻¹; MS el m/z 343 (M+); CHN calcd for C₂₃H₂₁NO₂

Example No. 20 5-Benzylxy-3-methyl-2-(4-trifluoromethoxy-phenyl)-1H-indole

Mp = 127 - 128°C; ¹H NMR (DMSO) 11.07 (s, 1 H), 7.77 - 7.74 (dd, 2 H, J = 1.8 Hz, J = 5.0 Hz), 7.50 - 7.48 (d, 4 H, J = 8.3 Hz), 7.42 - 7.25 (m, 4 H), 7.14 - 7.13 (d, 1 H, J = 2.2 Hz), 6.87 - 6.83 (dd, 1 H, J = 2.3 Hz, J = 6.3 Hz), 5.13 (s, 2 H), 2.37 (s, 3 H); IR (KBr) 3360, 1600 cm⁻¹; MS el m/z 396 (M+); CHN calcd for C₂₃H₁₈F₃NO₂

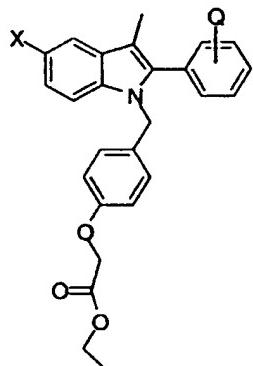
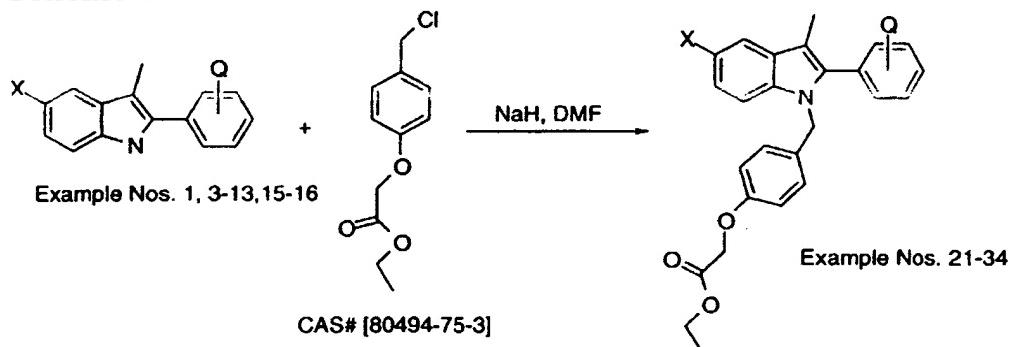
3-Methylindole acetic acid ethyl esters**Scheme 9**

Table 2

No. 21	H	H
No. 22	OBn	H
No. 23	OBn	4'-OMe
No. 24	OMe	4'-OMe
No. 25	OBn	4'-OEt
No. 26	OBn	4'-OBn
No. 27	OBn	4'-F
No. 28	OBn	3'-OMe, 4'-OBn
No. 29	OBn	4'-O-iPr
No. 30	OBn	3',4'-OCH ₂ O-
No. 31	OBn	4'-OCp
No. 32	OBn	4'-CF ₃
No. 33	OBn	4'-Cl
No. 34	OBn	2'-OMe, 4'-OMe

Experimental Procedure For 3-Methylindole Acetic Acid Ethyl Esters Synthesis Method 3 Illustrated For Example No. 26

{4-[5-Benzylxy-2-(4-benzylxy-phenyl)-3-methyl-indol-1-ylmethyl]-phenoxy}-acetic acid ethyl ester

A solution of 5-Benzylxy-2-(4-benzylxy-phenyl)-3-methyl-1H-indole (indole example No. 7) (32g, 77 mmol) in DMF (0.15 L) was cooled to 0°C and treated with sodium hydride (2.2 g, 89 mmol). The reaction was stirred for 20 minutes and then the benzyl chloride CAS No. [80494-75-3] (29g, 127 mmol) was added and the reaction stirred for 18 hours at room temperature. The reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate was washed with brine and dried over magnesium sulfate. The ethyl acetate was concentrated and triturated with ether to obtain 21 g of a white solid. The filtrate was concentrated and triturated with ether to give an additional 7 g of white solid for a total yield of 28 g: Mp = 129-131°C; ¹H NMR (DMSO) 7.47 (d, 4 H, J = 7.2 Hz), 7.39 (q, 4 H, J = 7.9 Hz), 7.36-7.32 (m, 1 H), 7.29 (d, 2 H, J = 8.8 Hz), 7.19 (d, 1 H, J = 9.0 Hz), 7.13-7.09 (m, 4 H), 6.80 (dd, 1 H, J = 8.8, 2.4 Hz), 6.73 (s, 4 H), 5.16 (s, 2 H), 5.13 (s, 2 H), 5.11 (s, 2 H), 4.66 (s, 2 H), 4.11 (q, 2 H, J = 7.2 Hz), 2.15 (s, 3 H), 1.16 (t, 3 H, J = 7.2 Hz); MS el m/z 612.

Physical Data For Indole Ethyl Esters

The following indole alkylation products were prepared according to scheme 9 using method 3 with the appropriately substituted 3-methyl indole selected from (No. 1-No. 16) as the starting material.

Example No. 21 {4-[2-Phenyl-3-methyl-indol-1-ylmethyl]-phenoxy}-acetic acid ethyl ester

Oil; ¹H NMR (DMSO) 7.57 - 7.30 (m, 7 H), 7.13 - 7.02 (m, 2 H), 6.77 - 6.70 (m, 4 H), 5.22 (s, 2 H), 4.65 (s, 2 H), 4.09 (q, 2 H, J = 7.2 Hz), 2.20 (s, 3 H), 1.15 (t, 3 H, J = 7.0 Hz); MS el m/z 399 (M+).

Example No. 22 {4-[5-Benzylxyloxy-2-phenyl-3-methyl-indol-1-ylmethyl]-phenoxy}-acetic acid ethyl ester

Oil; ^1H NMR(DMSO) 7.50 - 7.40 (m, 10 H), 7.22 (d, 1 H, J = 8.4Hz), 7.14 (d, 1H, J = 2.5Hz), 6.83 (d, 1 H, J = 2.5 Hz), 6.72 (s, 4 H), 5.18 (s, 2 H), 5.11 (s, 2 H), 4.65 (s, 2 H), 4.10 (q, 2 H, J = 7.2 Hz), 2.16 (s, 3 H), 1.14 (t, 3 H, J = 7.0Hz); MS el m/z 505 (M+).

Example No. 23 {4-[5-Benzylxyloxy-2-(4-methoxy-phenyl)-3-methyl-indol-1-ylmethyl]-phenoxy}-acetic acid ethyl ester

10 Mp = 90 - 96°C; ^1H NMR (DMSO) 7.47 (d, 2 H, J = 6.8 Hz), 7.41 - 7.37 (m, 2 H), 7.33 - 7.27 (m, 3 H), 7.19 (d, 1 H, J = 8.8 Hz), 7.12 (d, 1 H, J = 2.4 Hz), 7.03 (d, 2 H, J = 8.8 Hz), 6.80 (dd, 1 H, J = 8.8 Hz, 2.4 Hz), 6.74 (s, 4 H), 5.16 (s, 2 H), 5.11 (s, 2 H), 4.65 (s, 2 H), 4.11 (q, 2 H, J = 7.0 Hz), 3.79 (s, 3 H), 2.15 (s, 3 H), 1.16 (t, 3 H, J = 7.0 Hz); IR (KBr) 2990, 2900, 1760, 1610 cm⁻¹; MS FAB m/z 536 (M+H⁺).

Example No. 24 {4-[5-Methoxy-2-(4-methoxy-phenyl)-3-methyl-indol-1-ylmethyl]-phenoxy}-acetic acid ethyl ester

15 Mp = 109-113°C; ^1H NMR (DMSO) 7.27 (d, 2 H, J = 8.8Hz), 7.17 (d, 1 H, J = 8.8 Hz), 7.17 (d, 1 H, J = 8.8 Hz), 7.03 (d, 2 H, J = 8.6 Hz), 6.99 (d, 1 H, J = 2.5 Hz), 6.78 - 6.70 (m, 5 H), 5.15 (s, 2H), 4.65 (s, 2 H), 4.11 (q, 2 H, J = 7.0 Hz), 3.78 (s, 3 H), 3.76 (s, 3 H), 2.15 (s, 3 H), 1.15 (t, 3 H, J = 7.1 Hz); MS el m/z 459 (M+).

Example No. 25 {4-[5-Benzylxyloxy-2-(4-ethoxy-phenyl)-3-methyl-indol-1-ylmethyl]-phenoxy}-acetic acid ethyl ester

20 Mp = 113-115°C; ^1H NMR (DMSO) 7.45 (d, 2 H, J = 7.3 Hz), 7.40 - 7.25 (m, 5 H), 7.17 (d, 1 H, J = 8.8 Hz), 7.11 (d, 1 H, J = 2.2 Hz), 7.01 (d, 2 H, J = 6.8 Hz), 6.78 (dd, 1 H, J = 8.8Hz, J = 2.4 Hz), 6.73 (s, 4 H), 5.15 (s, 2 H), 5.10 (s, 2 H), 4.65 (s, 2 H), 4.15 - 4.01 (m, 4 H), 2.14 (s, 3H), 1.33 (t, 3 H, J = 5.7 Hz), 1.16 (t, 3 H, J = 7.1 Hz); MS el m/z 549 (M+).

Example No. 27 {4-[5-Benzylxyloxy-2-(4-fluoro-phenyl)-3-methyl-indol-1-ylmethyl]-phenoxy}-acetic acid ethyl ester

25 ^1H NMR (DMSO) 7.50 - 7.15 (m, 16 H), 5.20 (s, 2 H), 5.12 (s, 2 H), 4.62 (s, 2 H), 4.13 (q, 2 H, J = 7.1 Hz), 2.18 (s, 3 H), 1.20 (t, 3 H, J = 7.1 Hz).

Example No. 28 {4-[5-Benzylxyloxy-2-(3-methoxy-4-henzyloxy)-3-methyl-indol-1-ylmethyl]-phenoxy}-acetic acid ethyl ester

30 Foam; ^1H NMR (DMSO) 7.50 - 7.30 (m, 10 H), 7.22 (d, 2H, J = 9.1 Hz), 7.13 (d, 2 H, J = 8.6 Hz), 6.85 - 6.70 (m, 6 H), 5.17 (s, 2H), 5.13 (s, 2H), 5.11 (s, 2 H), 4.66 (s, 2 H), 4.14 (m, 2H), 3.61 (s, 3 H), 2.17 (s, 3 H), 1.16 (t, 3 H, J = 7.0 Hz).

Example No. 29 {4-[5-Benzylxyloxy-2-(4-isopropoxy-phenyl)-3-methyl-indol-1-ylmethyl]-phenoxy}-acetic acid ethyl ester

35 Oil; ^1H NMR (DMSO) 7.46 (d, 2H, J = 7.7 Hz), 7.42 - 7.28 (m, 3 H), 7.25 (d, 2 H, J = 8.7 Hz), 7.17 (d, 1 H, J = 8.7 Hz), 7.11 (d, 1 H, J = 2.4 Hz), 6.99 (d, 2 H, J = 8.6 Hz), 6.79 (dd, 1 H, J = 2.4 Hz, 8.8 Hz), 6.73 (s, 4 H), 5.15 (s, 2 H), 5.10 (s, 2 H), 4.70 - 4.60 (m, 3 H), 4.10 (q, 2 H, J = 7.0 Hz), 2.15 (s, 3 H), 1.27 (d, 6 H, J = 5.9 Hz), 1.16 (t, 3 H, J = 7.1 Hz); MS el m/z 563 (M+).

Example No. 30 {4-[5-Benzylxyloxy-2-(3,4-methylenedioxy-benzylxyloxy)-3-methyl-indol-1-ylmethyl]-phenoxy}-acetic acid ethyl ester

40 Oil; ^1H NMR (DMSO) 7.45 (d, 2 H, J = 7.0 Hz), 7.37 (m, 2 H), 7.32 (m, 1 H), 7.19 (d, 1H, J = 8.8 Hz), 7.11 (d, 1 H, J = 2.2 Hz), 7.00 (d, 1 H, J = 7.9 Hz), 6.90 (d, 1 H, 5.0 Hz), 6.82 - 6.75 (m, 6H), 6.07 (s, 2H), 5.16 (s, 2 H), 5.10 (s, 2H), 4.65 (s, 2 H), 4.10 (m, 2 H), 2.15 (s, 3 H), 1.15 (t, 3 H, J = 7.0 Hz); MS el m/z 549 (M+).

Example No. 31 {4-[5-Benzylxyloxy-2-(4-cyclopentyloxy-phenyl)-3-methyl-indol-1-ylmethyl]-phenoxy}-acetic acid ethyl ester

Mp = 96-98°C; ^1H NMR (DMSO) 7.47 (d, 1 H, J = 7.2 Hz), 7.40 - 7.36 (m, 2 H), 7.33 - 7.30 (m, 1 H), 7.26 (m, 2 H), 7.18 (d, 1 H, J = 8.8 Hz), 7.11 (d, 1 H, J = 2.4 Hz), 6.98 (d, 2 H, J = 8.8 Hz), 6.79 (dd, 1 H, J = 8.8 Hz, 2.4 Hz), 6.74 (s, 5 H), 5.15 (s, 2 H), 5.11 (s, 2 H), 4.86 - 4.80 (m, 1 H), 4.66 (s, 2 H), 4.13 (q, 2 H, J = 7.2 Hz), 2.15 (s, 3 H), 1.98 - 1.85 (m, 2 H), 1.79 - 1.65 (m, 4 H), 1.62-1.55 (m, 2 H), 1.16 (t, 3 H, J = 7.0 Hz); IR (KBr) 2950, 2910, 2890, 1760, 1610 cm^{-1} ; MS el m/z 589 (M+); CHN calcd for C₂₇H₃₃O₃N: C:77.39 H:6.67 N: 2.38 Found: C:76.76 H:6.63 N:2.27.

Example No. 32 {4-[5-Benzylxyloxy-3-methyl-2-(4-trifluoromethyl-phenyl)-indol-1-ylmethyl]-phenoxy}-acetic acid ethyl ester

Mp = 221°C; ^1H NMR (DMSO) 7.83 (d, 2 H, J = 8.1 Hz), 7.60 (d, 2 H, J = 7.9 Hz), 7.48 (d, 2 H, J = 8.4 Hz), 7.40 -7.36 (m, 4 H), 7.18 (d, 1 H, J = 2.4 Hz), 6.86 (dd, 1 H, J = 8.8 Hz, 2.4 Hz), 6.72 (s, 4 H), 5.21 (s, 2 H), 5.12 (s, 2 H), 4.65 (s, 2 H), 4.11 (q, 2 H, J = 7.2 Hz), 2.20 (s, 3 H), 1.16 (t, 3 H, J = 7.0 Hz); IR (KBr) 2920, 1730 cm^{-1} ; MS el m/z 573 (M+); CHN calcd for C₃₄H₃₀F₃NO₄ + 0.25 H₂O.

Example No. 33 {4-[5-Benzylxyloxy-2-(4-chlorophenyl)-3-methyl-indol-1-ylmethyl]-phenoxy}-acetic acid ethyl ester

Mp = 99-101°C; ^1H NMR (DMSO) 7.52 (d, 2 H, J = 8.6Hz), 7.46 (d, 2 H , J = 6.8 Hz), 7.42 - 7.38 (m ,4 H), 7.36 (m , 1H), 7.25 (d ,1 H , J = 9.0Hz),7.14 (d , 1 H , J = 2.4Hz), 6.83 (dd , 1.H , J = 8.8Hz , J = 2.5 Hz), 6.72 (s, 4 H), 5.18 (s , 2 H), 5.11 (s , 2 H), 4.65 (s , 2 H), 4.11 (q , 2 H, J = 7.2 Hz), 2.16 (s , 3 H), 1.15 (t, 3H , J = 7.2 Hz); MS el m/z 539 (M+); CHN calc for C₃₃H₃₀ClNO₄.

Example No. 34 {4-[5-Benzylxyloxy-2-(2,4-dimethoxy)-3-methyl-indol-1-ylmethyl]-phenoxy}-acetic acid ethyl ester

Oil; ^1H NMR (DMSO) 7.30 - 6.45 (m, 15 H), 4.95 (s, 2 H), 4.75 - 4.65 (m, 2 H), 4.50 (s, 2 H), 3.97 (q, 2 H, J = 7.1 Hz), 3.65 (s, 3 H), 3.51 (s, 3 H), 1.87 (3 H), 1.01 (t, 3 H, J = 7.1 Hz).

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3-Methylindole phenylethanols

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Scheme 10

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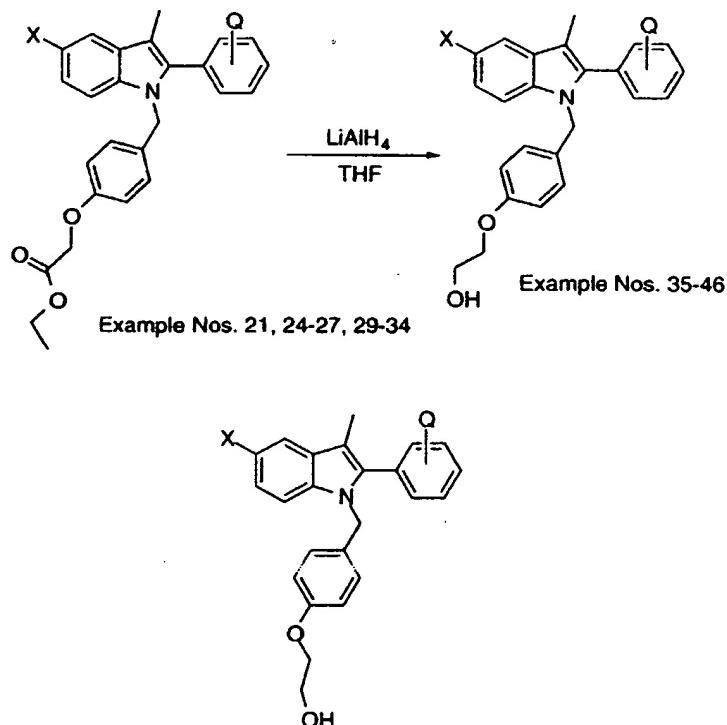


Table 3

No. 35	H	H
No. 36	OMe	4'-OMe
No. 37	OBn	4'-OEt
No. 38	OBn	4'-OBn
No. 39	OBn	4'-F
No. 40	OBn	3',4'-OCH ₂ O-
No. 41	OBn	4'-O-iPr
No. 42	OBn	4'-OCp
No. 43	OBn	4'-CF ₃
No. 44	OBn	4'-CH ₃
No. 45	OBn	4'-Cl
No. 46	OBn	2'-OMe, 4'-OMe

Experimental Procedure For 3-Methylindole Phenethanols Synthesis Method 4 Illustrated For Example No. 382-[4-[5-Benzylxy-2-(4-benzylxy-phenyl)-3-methyl-indol-1-ylmethyl]-phenoxy]-ethanol

A solution of No. 26 from previous step (5.5 g, 8.8 mmol) in THF (50 mL) was cooled to 0°C and a solution of LiAlH₄ (10mL, 1 M) in THF was added dropwise. After 30 minutes at 0°C the reaction was carefully quenched with water, and partitioned between EtOAc and 1 N HCl. The EtOAc was dried with MgSO₄, concentrated, and chromatographed on silica gel EtOAc/hexane (2:3) to yield 4.0 g of No. 38 as a white foam: ¹H NMR (DMSO) 7.48-7.46 (m, 4 H), 7.42-7.27 (m, 8 H), 7.20 (d, 1 H, J = 8.8 Hz), 7.12-7.10 (m, 3 H), 6.80 (dd, 1 H, J = 8.8, 2.4 Hz), 6.73 (s, 4 H), 5.15 (s, 2 H), 5.13 (s, 2 H), 5.11 (s, 2 H), 4.80 (t, 1 H, J = 5.5 Hz), 3.86 (t, 2 H, J = 4.8 Hz), 3.63 (q, 2 H, J = 5.3 Hz), 2.15 (s, 3 H).

Physical Data For Indole Phenethanols

Following compounds were made according to scheme 10 and method 4 using the appropriately substituted indole ethyl ester selected from No. 21- No. 34.

Example No. 35 2-[4-[2-phenyl-3-methyl-indol-1-ylmethyl]-phenoxy]-ethanol

Oil; ¹H NMR (DMSO) 7.57 - 7.32 (m, 7 H), 7.13 - 7.02 (m, 2 H), 6.74 (s, 4 H), 5.21 (s, 2 H), 4.80 (s, 1 H), 3.86 - 3.83 (m, 2 H), 3.62 (s, 2 H), 2.20 (s, 3 H); MS el m/z 357 (M+).

Example No. 36 2-[4-[5-methoxy-2-(4-methoxy-phenyl)-3-methyl-indol-1-ylmethyl]-phenoxy]-ethanol

Oil; ¹H NMR (DMSO) 7.27 (d, 2 H, J = 8.8Hz), 7.17 (d, 1 H, J = 8.8 Hz), 7.03 (d, 2 H J = 8.6 Hz) , 6.99 (d, 1 H, J = 2.5 Hz), 6.78 - 6.70 (m, 5 H) , 5.14 (s, 2 H), 4.80 (brs, 1H), 3.85 (t, 2 H, J = 5.0 Hz), 3.78 (s, 3H), 3.76 (s, 3 H), 3.63 (t, 2H , J = 5.0 Hz), 2.16 (s, 3H); MS el m/z 417 (M+).

Example No. 37 2-[4-[5-benzylxy-2-(4-ethoxy-phenyl)-3-methyl-indol-1-ylmethyl]-phenoxy]-ethanol

Foam; ¹H NMR (DMSO) 7.45 (d , 2 H , J =7.3 Hz), 7.40 - 7.25 (m, 5 H), 7.17 (d , 1 H , J = 8.8 Hz), 7.11 (d, 1 H, J =2.2 Hz), 7.01 (d, 2 H , J = 6.8 Hz), 6.78 (dd , 1 H , J = 8.8Hz, J = 2.4 Hz), 6.73 (s , 4H), 5.15 (s, 2 H), 5.10 (s , 2H),

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4.80 (brs, 1 H), 4.06 (q , 2 H, J = 6.8 Hz), 3.85 (t , 2 H, J J = 5.0 Hz), 3.63 (t , 2H , J = 4.8 Hz), 2.14 (s , 3H), 1.33 (t, 3H, J = 6.9 Hz); MS el m/z 507 (M+).

Example No. 39 2-[4-[5-benzyloxy-2-(4-flouro-phenyl)-3-methyl-indol-1-ylmethyl]-phenoxy]-ethanol

⁵ ¹H NMR (DMSO) 7.40 - 6.60 (m, 16 H), 5.10 (s, 1 H), 5.07 (s, 2 H), 5.02 (s, 2 H), 3.76 (t, 2 H, J = 4.9 Hz), 3.53 (t, 2 H, J = 5.0 Hz), 2.06 (s, 3 H).

Example No. 40 2-[4-[5-benzyloxy-2-(3,4-methylenedioxy-phenyl)-3-methyl-indol-1-ylmethyl]-phenoxy]-ethanol

¹⁰ Oil; ¹H NMR (DMSO) 7.45 (d, 2 H, J = 7.0 Hz), 7.37 (m , 2 H), 7.32 (m, 1 H), 7.19 (d, 1H, J = 8.8 Hz), 7.11 (d, 1 H, J = 2.2 Hz), 7.00 (d, 1 H, J = 7.9 Hz), 6.90 (d, 1 H, 5.0 Hz), 6.82 - 6.75 (m, 6H), 6.07 (s, 2 H), 5.16 (s , 2 H), 5.10 (s , 2 H), 3.86 (t, 2 H , J = 5.0 Hz), 3.63 (t , 2 H , J = 5.0 Hz), 2.15 (s, 3 H); MS el m/z 507 (M+).

Example No. 41 2-[4-[5-BenzylOxy-2-(4-isopropoxy-phenyl)-3-methyl-indol-1-ylmethyl]-phenoxy]-ethanol

¹⁵ Foam; ¹H NMR (DMSO) 7.46 (d, 2H, J = 7.7 Hz), 7.42 - 7.28 (m, 3 H), 7.25 (d, 2 H, J = 8.7 Hz), 7.17 (d, 1 H, J = 8.7 Hz), 7.11 (d, 1 H, J = 2.4 Hz), 6.99 (d, 2 H, J = 8.6 Hz), 6.79 (dd, 1 H, J = 2.4 Hz, 8.8 Hz), 6.73 (s, 4 H), 5.14 (s, 2 H), 5.10 (s, 2 H), 4.80 (bs, 1 H), 4.70 - 4.60 (m, 1 H), 3.85 (t, 2 H, J = 4.8 Hz), 3.63 (t, 2 H, J = 5.1 Hz), 2.13 (s, 3 H), 1.30 (d, 6 H, J = 5.9 Hz); MS el m/z 521 (M+).

Example No. 42 2-[4-[5-BenzylOxy-2-(4-cyclopentyloxy-phenyl)-3-methyl-indol-1-ylmethyl]-phenoxy]-ethanol

²⁵ Mp = 129-131°C; ¹H NMR (DMSO) 7.47 (d, 2 H, J = 7.2 Hz), 7.38 (t, 2 H, J = 7.2 Hz), 7.33 - 7.28 (m, 1 H), 7.25 (d, 2 H, J = 8.8 Hz), 7.18 (d, 1 H, J = 8.8 Hz), 7.11 (d, 1 H, J = 2.4 Hz), 6.98 (d, 2 H, J = 8.8 Hz), 6.79 (dd, 1 H, J = 8.8 Hz, 2.4 Hz), 6.74 (s, 4H), 5.15 (s, 2 H), 5.11 (s, 2 H), 4.84 - 4.80 (m, 1 H), 4.79 (t, 1 H, J = 5.7 Hz), 3.86 (t, 2 H, J = 4.8 Hz), 3.63 (q, 2 H, J = 5.1 Hz), 2.15 (s, H), 1.96 - 1.87 (m, 2 H), 1.77 - 1.65 (m, 4 H), 1.62-1.53 (m, 2 H); IR (KBr) 3490 br, 2920, 1620 cm⁻¹; MS el m/z 547 (M+).

³⁰ **Example No. 43 2-[4-[5-BenzylOxy-2-(4-trifluoromethyl-phenyl)-3-methyl-indol-1-ylmethyl]-phenoxy]-ethanol**

Foam; ¹H NMR (DMSO) 7.83 (d, 2 H, J = 8.1 Hz), 7.59 (d, 2 H, J = 7.9 Hz), 7.47 (d, 2 H, J = 8.3 Hz), 7.42 - 7.36 (m, 2 H), 7.35 - 7.29 (m, 2 H), 7.18 (d, 1 H, J = 2.4 Hz), 6.87 (dd, 1 H, J = 8.1 Hz, 2.4 Hz), 6.77 - 6.68 (m, 4 H), 5.21 (s, 2 H), 5.12 (s, 2 H), 4.81 (br s, 1 H), 3.85 (t, 2 H, J = 5.1 Hz), 3.63 (t, 2 H, J = 5.1 Hz), 2.19 (s, 3 H); MS el m/z 531.

Example No. 44 2-[4-[5-BenzylOxy-2-(4-methyl-phenyl)-3-methyl-indol-1-ylmethyl]-phenoxy]-ethanol

⁴⁰ Oil; ¹H NMR (DMSO) 7.46 (d, 2 H, J = 7.2 Hz), 7.45 - 7.18 (m, 8 H), 7.12 (d, 1 H, J = 2.4 Hz), 6.81 (dd, 1 H, J = 2.4 Hz, 8.6 Hz), 6.73 (s, 4 H), 5.15 (s, 2 H), 5.10 (s, 2 H), 4.80 (bs, 1 H), 3.85 (t, 2 H, J = 4.8 Hz), 3.63 (t, 2 H, J = 4.9 Hz), 2.34 (s, 3 H), 2.15 (s, 3 H); MS el m/z 477 (M+).

Example No. 45 2-[4-[5-BenzylOxy-2-(4-chloro-phenyl)-3-methyl-indol-1-ylmethyl]-phenoxy]-ethanol

⁴⁵ Mp = 110 - 113°C; ¹H NMR (DMSO) 7.52 (d , 2 H, J = 8.6Hz), 7.46 (d, 2 H, J = 6.8Hz), 7.38 (m,4 H), 7.42 - 7.37 (m, 1 H), 7.25 (d, 1 H, J = 9.0Hz), 7.14 (d, 1 H, J = 2.4Hz), 6.83 (dd,1H, J = 8.8Hz, = 2.5 Hz), 6.76 - 6.70 (m, 4 H), 5.17 (s , 2 H), 5.11 (s ,2H), 3.85 (t, 2H , J = 5.2Hz), 3.63 (t, 2H, J= 5.0 Hz), 2.16 (s , 3 H); MS el m/z 497 (M+).

⁵⁰ **Example No. 46 2-[4-[5-BenzylOxy-2-(2,4-dimethoxy-phenyl)-3-methyl-indol-1-ylmethyl]-phenoxy]-ethanol**

Oil; ¹H NMR (DMSO) 7.46 (d, 2 H, J = 7.5 Hz), 7.39 - 7.35 (m, 2 H), 7.31 - 7.28 (m, 1H), 7.16 - 7.06 (m, 3 H), 6.82 - 6.72 (m, 5 H), 6.68 (d, 1 H, J = 2.2 Hz), 6.61 (dd, 1 H, J = 2.4 Hz, 8.3 Hz), 5.0 (s, 1 H), 4.88 (s, 2 H), 4.85 (d, 1H, J = 6.3 Hz), 4.69 (d, 1 H, J = 6.3 Hz), 3.63 (t, 2 H, J = 6.9 Hz), 3.58 (s, 3 H), 3.46 (s, 3 H), 3.40 (t, 2 H, J = 6.9 Hz), 1.80 (s, 3 H).

Data for 3-methylindole phenylethyl bromides

Scheme 11

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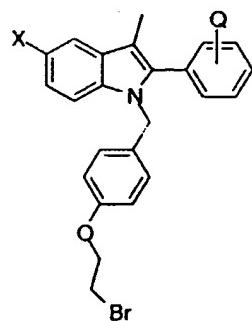
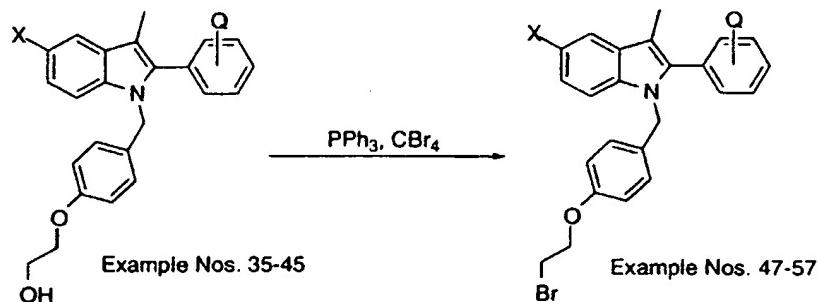
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Table 4

No. 47	H	H
No. 48	OMe	4'-OMe
No. 49	OBn	4'-OEt
No. 50	OBn	4'-OBn

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Table 4 (Cont'd)

No.	Substituent	Product
No. 51	OBn	4'-F
No. 52	OBn	3',4'-OCH ₂ O-
No. 52a	OBn	3'-OMe, 4'-OBn
No. 53	OBn	4'-O-iPr
No. 54	OBn	4'-OCp
No. 55	OBn	4'-CF ₃
No. 56	OBn	4'-CH ₃
No. 57	OBn	4'-Cl

Experimental Procedure For 3-Methylindole Phenethyl bromide Synthesis Method 5 Illustrated For Example No. 50

Example No. 50

5-Benzylxy-2-(4-benzylxy-phenyl)-1-[4-(2-bromo-ethoxy)-benzyl]-3-methyl-1H-indole

To a solution of example No. 38 (3.3 g, 5.8 mmol) in THF (50 mL) was added CBr₄ (2.9 g, 8.7 mmol) and PPH₃ (2.3 g, 8.7 mmol). The reaction was stirred at rt for 3 h and then concentrated and chromatographed on silica gel using a gradient elution from EtOAc/hexane (1:4) to EtOAc to give 3.2 g of a white solid: Mp = 131-134°C; ¹H NMR (DMSO) 7.64-7.30 (m, 10 H), 7.29 (d, 2 H, J = 8.8 Hz), 7.20 (d, 1 H, J = 8.8 Hz), 7.12-7.09 (m, 3 H), 6.80 (dd, 1 H, J = 8.8, 2.4 Hz), 6.77-6.73 (m, 4 H), 5.16 (s, 2 H), 5.13 (s, 2 H), 5.11 (s, 2 H), 4.20 (t, 2 H, J = 5.3 Hz), 3.73 (t, 2 H, J = 5.5 Hz), 2.15 (s, 3 H); MS FAB 631/633 (M+H+, Br present).

Physical Data for Indole Phenethyl Bromides

The following compounds were made according to scheme 11 as described in Method 5 using the appropriately substituted indole selected from No. 35- No. 45.

Example No. 47 1-[4-(2-bromo-ethoxy)-benzyl]-2-phenyl-3-methyl-1H-indole

Oil; ¹H NMR (DMSO) 7.57 - 7.32 (m, 7 H), 7.13 - 7.02 (m, 2 H), 6.74 (s, 4 H), 5.21 (s, 2 H), 4.19 (t, 2 H, J = 5.2 Hz), 3.71 (t, 2 H, J = 5.5 Hz), 2.20 (s, 3 H); MS el m/z 419 (M+).

Example No. 48 5-Methoxy-2-(4-methoxy-phenyl)-1-[4-(2-bromo-ethoxy)-benzyl]-3-methyl-1H-indole

Oil; ¹H NMR (DMSO) 7.27 (d, 2 H, J = 8.8 Hz), 7.17 (d, 1 H, J = 8.8 Hz), 7.03 (d, 2 H, J = 8.6 Hz), 6.99 (d, 1 H, J = 2.5 Hz), 6.80 - 6.69 (m, 5 H), 5.14 (s, 2 H), 4.19 (t, 2 H, J = 5.4 Hz), 3.78 (s, 3 H), 3.76 (s, 3 H), 3.72 (t, 2 H, J = 5.5 Hz), 2.16 (s, 3 H); MS el m/z 479 (M+).

Example No. 49 5-Benzylxy-2-(4-ethoxy-phenyl)-1-[4-(2-bromo-ethoxy)-benzyl]-3-methyl-1H-indole

Mp = 118-120°C; ¹H NMR (DMSO) 7.45 (d, 2 H, J = 7.3 Hz), 7.41 - 7.26 (m, 5 H), 7.17 (d, 1 H, J = 8.8 Hz), 7.11 (d, 1 H, J = 2.2 Hz), 7.01 (d, 2 H, J = 6.8 Hz), 6.78 (dd, 1 H, J = 8.8 Hz, J = 2.4 Hz), 6.78 - 6.74 (m, 4 H), 5.15 (s, 2 H), 5.10 (s, 2 H), 4.22 - 4.18 (m, 2 H), 4.04 (q, 2 H, J = 6.8 Hz), 3.72 (t, 2 H, J = 5.5 Hz), 2.14 (s, 3 H), 1.33 (t, 3 H, J = 7.0 Hz); MS el m/z 569 (M+).

Example No. 51 5-Benzylxyloxy-1-[4-(2-bromo-ethoxy)-benzyl]-2-(4-fluoro-phenyl)-3-methyl-1H-indole

Mp = 114-116°C; ¹H NMR (DMSO) 7.47 (m, 2 H), 7.45 - 7.20 (m, 8 H), 7.14 (d, 1 H, J = 2.4 Hz), 6.83 (dd, 1 H, J = 2.7 Hz, 9.0 Hz), 6.80 - 6.70 (m, 4 H), 5.16 (s, 2 H), 5.11 (s, 2 H), 4.19 (t, 2 H, J = 5.27 Hz), 3.72 (t, 2 H, J = 6.4 Hz), 2.15 (s, 3 H); MS el m/z 543 (M+); CHN calc for C₃₁H₂₇BrFNO₂.

Example No. 52 2-Benzol[1-3]dioxy-5-yl-5-benzylxyloxy-1-[4-(2-bromo-ethoxy)-benzyl]-3-methyl-1H-indole

Mp = 133-136°C; ¹H NMR (DMSO) 7.45 (d, 2 H, J = 7.0 Hz), 7.41-7.38 (m, 2 H), 7.35-7.30 (m, 1 H), 7.19 (d, 1 H, J = 8.8 Hz), 7.11 (d, 1 H, J = 2.2 Hz), 7.00 (d, 1 H, J = 7.9 Hz), 6.90 (d, 1 H, 1.4 Hz), 6.82 - 6.78 (m, 2H), 6.77 (s, 4 H), 6.07 (s, 2 H), 5.16 (s, 2 H), 5.10 (s, 2 H), 4.20 (t, 2 H, J = 5.5Hz), 3.73 (t, 2H, J = 5.2Hz), 2.15 (s, 3H); MS el m/z 569 (M+).

Example No. 52a 5-Benzylxyloxy-1-[4-(2-bromo-ethoxy)-benzyl]-2-(3-methoxy-4-benzylxyloxy-phenyl)-3-methyl-1H-indole

Foam; ¹H NMR (DMSO) 7.47 - 7.42 (m, 4 H), 7.40 - 7.30 (m, 6 H), 7.20 (d, 1 H, J = 8.8 Hz), 7.12 - 7.10 (m, 2 H), 6.86 - 6.84 (m, 2 H), 6.81 (dd, 1 H, J = 8.8 Hz, 2.4 Hz), 6.78 (s, 4 H), 5.17 (s, 2 H), 5.11 (s, 2 H), 5.10 (s, 2 H), 4.20 (t, 2 H, J = 5.0 Hz), 3.72 (t, 2 H, J = 5.4 Hz), 3.63 (s, 3 H), 2.17 (s, 3 H); MS FAB m/z 662 (M+H+).

Example No. 53 5-Benzylxyloxy-1-[4-(2-bromo-ethoxy)-benzyl]-2-(4-isopropoxy-phenyl)-3-methyl-1H-indole

Mp = 125 - 128°C; ¹H NMR (DMSO) 7.46 (d, 2H, J = 7.7 Hz), 7.42 - 7.28 (m, 3 H), 7.25 (d, 2 H, J = 8.7 Hz), 7.17 (d, 1 H, J = 8.7 Hz), 7.11 (d, 1 H, J = 2.4 Hz), 6.99 (d, 2 H, J = 8.6 Hz), 6.79 (dd, 1 H, J = 2.4 Hz, 8.8 Hz), 6.73 (s, 4 H), 5.14 (s, 2 H), 5.10 (s, 2 H), 4.70 - 4.60 (m, 1 H), 4.19 (t, 2 H, J = 5.3 Hz), 3.72 (t, 2 H, J = 4.4 Hz), 2.13 (s, 3 H), 1.30 (d, 6 H, J = 5.9 Hz); MS el m/z 583 (M+).

Example No. 54 5-Benzylxyloxy-1-[4-(2-bromo-ethoxy)-benzyl]-2-(4-cyclopentyloxy-phenyl)-3-methyl-1H-indole

Mp = 110 - 112°C; 7.47 (d, 2 H, J = 7.0 Hz), 7.38 (t, 2 H, J = 7.0 Hz), 7.35 - 7.28 (m, 1 H), 7.25 (d, 2 H, J = 8.8 Hz), 7.18 (d, 1 H, J = 8.8 Hz), 7.11 (d, 1 H, J = 2.4 Hz), 6.98 (d, 2 H, J = 8.6 Hz), 6.79 (dd, 1 H, J = 8.6 Hz, 2.4 Hz), 6.78 - 6.74 (m, 4 H), 5.16 (s, 2 H), 5.11 (s, 2 H), 4.86 - 4.83 (m, 1 H), 4.20 (t, 2 H, J = 5.3 Hz), 3.73 (t, 2 H, J = 5.5 Hz), 2.15 (s, 3 H), 2.00 - 1.87 (m, 2 H), 1.79 - 1.65 (m, 4 H), 1.63 - 1.56 (m, 2 H); IR (KBr) 2950, 2910, 1610 cm⁻¹; MS el m/z 609, 611 (M+, Br present).

Example No. 55 5-Benzylxyloxy-1-[4-(2-bromo-ethoxy)-benzyl]-3-methyl-2-(4-trifluoromethyl-phenyl)-1H-indole

Mp = 106 - 109°C; ¹H NMR (DMSO) 7.83 (d, 2 H, J = 8.1 Hz), 7.60 (d, 2 H, J = 7.9 Hz), 7.35 - 7.29 (m, 2 H), 7.48 (d, 2 H, J = 8.6 Hz), 7.39 (t, 2 H, J = 7.0 Hz), 7.18 (d, 1 H, J = 2.2 Hz), 6.87 (dd, 1 H, J = 9.0 Hz, 2.6 Hz), 6.77 - 6.71 (m, 4 H), 5.22 (s, 2 H), 5.12 (s, 2 H), 4.20 (t, 2 H, J = 5.3 Hz), 3.72 (t, 2 H, J = 5.3 Hz), 2.20 (s, 3 H); IR (KBr) 2910, 2850, 1620 cm⁻¹; MS el m/z 595, 593 (M+).

Example No. 56 5-Benzylxyloxy-1-[4-(2-bromo-ethoxy)-benzyl]-3-methyl-2-(4-methyl-phenyl)-1H-indole

Mp = 82 - 95°C; ¹H NMR (DMSO) 7.46 (d, 2 H, J = 7.2 Hz), 7.45 - 7.18 (m, 8 H), 7.12 (d, 1 H, J = 2.4 Hz), 6.81 (dd, 1 H, J = 2.4 Hz, 8.6 Hz), 6.73 (s, 4 H), 5.15 (s, 2 H), 5.10 (s, 2 H), 4.19 (t, 2 H, J = 5.3 Hz), 3.72 (t, 2 H, J = 4.4 Hz), 2.34 (s, 3 H), 2.15 (s, 3 H); MS el m/z 539 (M+).

Example No. 57 5-Benzylxyloxy-1-[4-(2-bromo-ethoxy)-benzyl]-3-methyl-2-(4-chloro-phenyl)-1H-indole

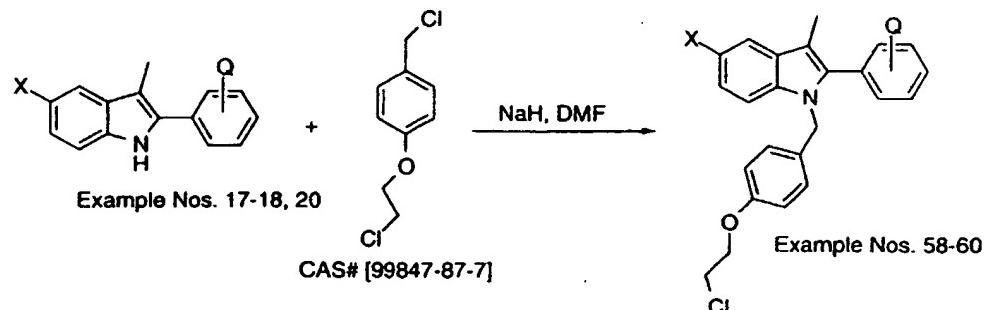
¹H NMR (DMSO) 7.52 (d ,2H, J = 8.6Hz),7.46 (d , 2H , J = 6.8Hz), 7.38 (m ,4 H),7.36 (m , 1H),7.25 (d, 1H , J = 9.0Hz),7.14 (d , 1H , J = 2.4Hz), 6.83 (dd , 1H , J = 8.8Hz , J = 2.5 Hz), 6.72 (m ,4H), 5.17 (s , 2H), 5.11 (s , 2H), 4.19 (t , 2H , J = 5.5 Hz), 3.72 (t , 2H , J = 5.5 Hz), 2.16 (s , 3H); MS el m/z 559 (M+).

Data for some 3-methylindole phenylethyl chlorides used as intermediates

Scheme 12

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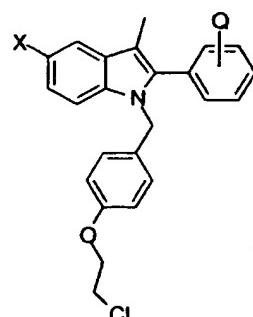


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Table 5

No. 58	OBn	3'-OBn
No. 59	OBn	3'-F, 4'-OBn
No. 60	OBn	4'-OCF ₃

Experimental Procedure For 3-Methylindole Phenethylchloride Synthesis Method 5a Illustrated For Example No. 585-Benzylxy-2-(3-benzylxy-phenyl)-1-[4-(2-chloro-ethoxy)-benzyl]-3-methyl-1H-indole

To a solution of 9.7 g (0.0231 mol) of 5-benzylxy-3-methyl-2-(3-benzylxy-phenyl)-1H-indole (indole example No. 17) in 80 mL of dry DMF was added 0.85 g of sodium hydride (60% in mineral oil). After allowing this mixture to stir for 30 minutes (until no more bubbling was indicated), 4.8 g of 1-chloromethyl-4-(2-chloro-ethoxy)-benzene CAS No. [99847-87-7] was added. The reaction mixture was allowed to react at room temperature overnight. 200 mL of ethyl acetate were added to the reaction mixture and then washed with water (3x 100 mL). The organic solution was collected, washed with saturated brine, removed, dried over magnesium sulfate, filtered and evaporated to dryness in a rotary evaporator. The product was recrystallized in ethyl acetate.

Mp = 125 - 127°C; ¹H NMR (DMSO) 7.48 - 7.46 (d, 2 H, J = 6.8 Hz), 7.40 - 7.35 (m, 7 H), 7.33 - 7.28 (m, 2 H), 7.23 - 7.21 (d, 1 H, J = 8.8 Hz), 7.13 - 7.12 (d, 1 H, J = 2.2 Hz), 7.07 - 7.04 (m, 1 H), 6.94 - 6.92 (d, 2 H, J = 6.1 Hz), 6.83-6.80

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(dd, 1 H, J = 2.5 Hz, J = 6.3 Hz), 6.78 - 6.72 (m, 4 H), 5.14 (s, 2 H), 5.11 (s, 2 H), 5.04 (s, 2 H), 4.13 - 4.10 (t, 2 H, J = 5. 1 Hz), 3.86 - 3.84 (t, 2 H, J = 5.1 Hz), 2.14 (s, 3 H); IR 3420, 2900 cm⁻¹; MS el m/z 587 (M+); CHN calcd for C₃₈H₃₄ClNO₃.

5 **Physical Data for Indole Phenethyl Chlorides**

The following compounds were made according to scheme 12 as described in Method 5a using the appropriately substituted indoles No. 18, No. 20.

10 **Example No. 59 5-BenzylOxy-2-(4-benzylOxy-3-fluoro-phenyl)-1-[4-(2-chloro-ethoxy)-benzyl]-3-methyl-1H-indole**

15 Mp = 88-91°C; ¹H NMR (DMSO) 7.49-7.43 (m, 4H), 7.43-7.28 (m, 7H), 7.26-7.21 (m, 2H), 7.13-7.09 (m, 2H), 6.88-6.72 (m, 5H), 5.21 (s, 2H), 5.18 (s, 2H), 5.11 (s, 2H), 4.13 (t, 2H, J = 5.2 Hz), 3.87 (t, 2H, J = 5.2 Hz), 2.16 (s, 3H); MS el m/z 605 (M+); CHN calcd for C₃₈H₃₃ClFNO₃.

Example No. 60 5-BenzylOxy-1-[4-(2-chloro-ethoxy)-benzyl]-3-methyl-2-(4-trifluoromethoxy-phenyl)-1H-indole

20 Mp = 108 - 110°C; ¹H NMR (DMSO) 7.49 - 7.48 (m, 6 H), 7.40 - 7.25 (m, 4 H), 7.17-7.16 (d, 1 H, J = 2.9 Hz), 6.88 - 6.84 (m, 1 H), 6.77 - 6.72 (m, 4 H), 5.20 (s, 2 H), 5.14 - 5.13 (d, 2 H, J = 2.3 Hz), 4.16 - 4.11 (m, 2 H), 3.89 - 3.84 (m, 2 H), 2.19 - 2.17 (m, 3 H); IR 3400, 2900, 1600 cm⁻¹; MS el m/z 566 (M+); CHN calcd for C₃₂H₂₇ClF₃NO₃ + 0.25 H₂O.

Aminoethoxy indoles

25 **Scheme 13**

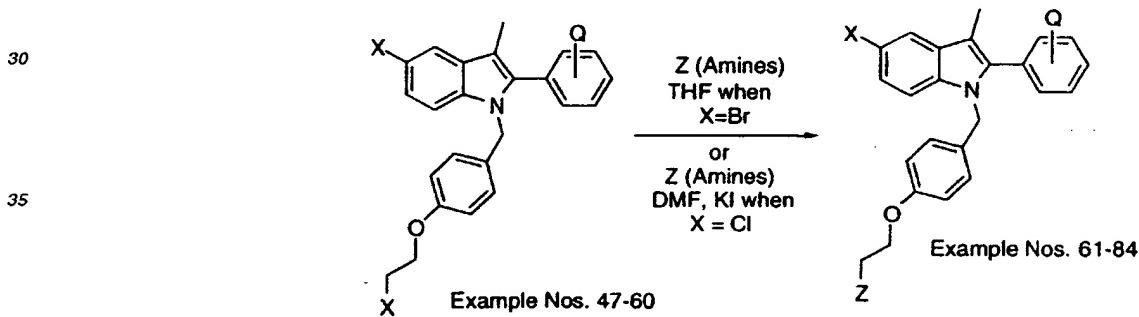


Table 6

5	No. 61	OBn	4'-OEt
10	No. 62	OBn	H
15	No. 63	OBn	4'-OBn
20	No. 64	OBn	4'-OBn
25	No. 65	OBn	4'-OBn

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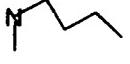
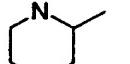
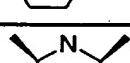
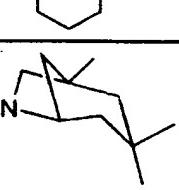
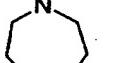
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Table 6 (Cont'd)

No. 66	OBn	4'-OBn	
No. 66a	OBn	4'-OBn	
No. 67	OBn	4'-OBn	
No. 68	OBn	4'-OBn	
No. 69	OBn	4'-OBn	
No. 70	OBn	4'-OBn	
No. 71	OBn	4'-OBn	
No. 71a	OBn	4'-OBn	
No. 72	OBn	4'-F	

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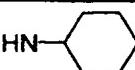
50

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Table 6 (Cont'd)

5	No. 72a	OBn	4'-F
10	No. 72b	OBn	4'-Cl
15	No. 73	OBn	3',4'-OCH ₂ O-
20	No. 74	OBn	4'-O-iPr
25	No. 75	OBn	4'-CH ₃
30	No. 76	OBn	3'-OBn
35	No. 77	OBn	3'-OBn
40	No. 78	OBn	4'-OBn,3'-F
45	No. 79	OBn	4'-OBn,3'-F

Table 6 (Cont'd)

No. 80	OBn	3'-OMe	
No. 81	OBn	4'-OCF ₃	
No. 82	OBn	4'-OBn	
No. 83	OBn	4'-OBn	
No. 84	OBn	3'-OMe	

Experimental Procedure For 3-Methyl aminoethoxyindole Synthesis Method 6 Illustrated For Example No. 63
Substitution of the Bromide

5-Benzylxy-2-(4-benzylxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole

A solution of example No. 50 (3.2 g, 5.0 mmol) in THF (50 mL) was treated with piperidine (5.0 mL, 50 mmol) and heated to reflux. After 5 hours, the reaction mixture was concentrated and taken up in EtOAc, washed with saturated NaHCO₃, dried over MgSO₄ and column chromatographed on silica gel using a gradient elution of EtOAc/Hexane to EtOAc. The product (2.7 g) was a white solid with a Mp = 93-95°C; ¹H NMR (DMSO) 7.48-7.46 (m, 4 H), 7.42-7.38 (m, 4 H), 7.38-7.32 (m, 2 H), 7.29 (d, 2 H, J = 8.8 Hz), 7.19 (d, 1 H, J = 9.0 Hz), 7.12-7.10 (m, 3 H), 6.80 (dd, 1 H, J = 8.8, 2.4 Hz), 6.73 (s, 4 H), 5.15 (s, 2 H), 5.13 (s, 2 H), 5.11 (s, 2 H), 3.93 (t, 2 H, J = 5.7 Hz), 2.60-2.50 (m, 2 H), 2.41-2.30 (m, 4 H), 2.15 (s, 3 H), 1.47-1.42 (m, 4 H), 1.36-1.32 (m, 2 H); MS FAB 637 (M+H⁺).

Alternative Procedure Method 6a Substitution of chlorides Synthesis illustrated for product No. 76

Example No. 76 5-Benzylxy-2-(3-benzylxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole

To a solution of 1.1 g (0.00953 mol) of 5-benzylxy-2-(3-benzylxy-phenyl)-1-[4-(2-chloro-ethoxy)-benzyl]-3-methyl-1H-indole (example No. 58) in 10 mL of DMF was added 1.1 mL (0.0112 mol) of piperidine, and 0.93 g (0.00561 mol) of potassium iodide. The reaction mixture was heated to ~40-50° C for 4 hours. After cooling the reaction mixture to room temperature, 150 mL of ethyl acetate were added and the mixture was washed with water (3 x 100 mL). The organic solution was collected, washed with saturated brine, removed, dried over magnesium sulfate, filtered and evaporated to yield 1.0 g of product of the product after purification.
 Mp = 125 - 126°C; ¹H NMR (DMSO) 7.48 - 7.45 (d, 2 H, J = 7.2 Hz), 7.41 - 7.35 (m, 7 H), 7.33 - 7.28 (m, 2 H), 7.23 - 7.21 (d, 1 H, J = 9.0 Hz), 7.13 - 7.12 (d, 1 H, J = 2.4 Hz), 7.06 - 7.03 (m, 1 H), 6.95 - 6.91 (m, 2 H), 6.83 - 6.80 (dd, 1 H, J = 2.4 Hz, J = 6.3 Hz), 6.75 - 6.70 (m, 4 H), 5.13 (s, 2 H), 5.11 (s, 2 H), 5.02 (s, 2 H), 3.93 - 3.90 (t, 2 H, J = 6.0 Hz), 2.56 - 2.53 (t, 2 H, J = 5.9 Hz), 2.49-2.48 (m, 4 H), 2.14 (s, 3 H), 1.46 - 1.40 (m, 4 H), 1.35 - 1.31 (m, 2 H); IR (KBr) 3400, 2900 cm⁻¹; MS el m/z 636 (M⁺); CHN calcd for C₄₃H₄₄N₂O₃ + 0.25 H₂O.

Physical data for the amine substituted compounds

The following compounds were prepared by scheme 13 using method 6. Except for examples No. 76- No. 84 which were prepared using method 6a.

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Example No. 61 5-Benzylxyloxy-2-(4-ethoxy-phenyl)-3-methyl-1-[4-(2piperidin-1-yl-ethoxy)-benzyl]-1H-indole

Mp = 188 - 191°C; ¹H NMR (DMSO) 7.45 (d, 2 H, J = 7.3 Hz), 7.40 - 7.25 (m, 5 H), 7.17 (d, 1 H, J = 8.8 Hz), 7.11 (d, 1 H, J = 2.2 Hz), 7.01 (d, 2 H, J = 6.8 Hz), 6.78 (dd, 1 H, J = 8.8 Hz, J = 2.4 Hz), 6.73 (s, 4 H), 5.15 (s, 2 H), 5.10 (s, 2 H), 4.05 (q, 2 H, J = 6.8 Hz), 3.93 (t, 2 H, J = 6.0 Hz), 2.55 (t, 2 H, J = 5.7 Hz), 2.41-2.35 (m, 4 H), 2.14 (s, 3 H), 1.46 - 1.40 (m, 4 H), 1.38 - 1.30 (m, 5 H); MS esl m/z 574 (M+).

Example No. 62 5-Benzylxyloxy-2-phenyl-3-methyl-1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-1H-indole

Oil; ¹H NMR (DMSO) 7.50-7.43 (m, 4 H), 7.42-7.37 (m, 5 H), 7.33-7.30 (m, 1 H), 7.22 (d, 1 H, J = 8.8 Hz), 7.14 (d, 1 H, J = 2.4 Hz), 6.81 (d, 1 H, J = 6.6 Hz), 6.72 (s, 4 H), 5.18 (s, 2 H), 5.11 (s, 2 H), 3.90 (t, 2 H, J = 6. Hz), 2.81-2.75 (m, 2 H), 2.68-2.59 (m, 4 H), 2.16 (s, 3 H), 1.58-1.43 (m, 8 H); MS esl m/z 544 (M+).

Example No. 64 5-Benzylxyloxy-2-(4-benzylxyloxy-phenyl)-3-methyl-1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-1H-indole

Mp = 106 - 107°C; ¹H NMR (DMSO) 7.47 (d, 4 H, J = 8.3 Hz), 7.41 - 7.36 (m, 4 H), 7.36 - 7.30 (m, 2 H), 7.29 (d, 2 H, J = 8.8 Hz), 7.19 (d, 1 H, J = 8.8 Hz), 7.14 - 7.10 (m, 3 H), 6.80 (dd, 1 H, J = 8.8 Hz), 6.73 (s, 4 H), 5.15 (s, 2 H), 5.13 (s, 2 H), 5.11 (s, 2 H), 3.90 (t, 2 H, J = 5.9 Hz), 2.76 (t, 2 H, J = 5.9 Hz), 2.64 - 2.56 (m, 4 H), 2.15 (s, 3 H), 1.58 - 1.44 (m, 8 H); MS FAB m/z 651 (M+H⁺).

Example No. 65 5-Benzylxyloxy-2-(4-benzylxyloxy-phenyl)-3-methyl-1-[4-(2-diisopropylamino-1-yl-ethoxy)-benzyl]-1H-indole

Mp = 148 - 150°C; ¹H NMR (DMSO) 7.47 (d, 4 H, J = 8.3 Hz), 7.41 - 7.36 (m, 4 H), 7.36 - 7.32 (m, 2 H), 7.28 (d, 2 H, J = 8.8 Hz), 7.19 (d, 1 H, J = 9.0 Hz), 7.13 - 7.08 (m, 3 H), 6.80 (dd, 1 H, J = 8.8 Hz, 2.4 Hz), 6.76 - 6.68 (m, 4 H), 5.14 (s, 2 H), 5.13 (s, 2 H), 5.11 (s, 2 H), 3.75 (t, 2 H, J = 7.0 Hz), 2.95 (m, 2 H), 2.67 (t, 2 H, J = 7.0 Hz), 2.15 (s, 3 H), 0.93 (d, 12 H, J = 6.4 Hz); MS FAB m/z 653 (M+H⁺).

Example No. 66 5-Benzylxyloxy-2-(4-benzylxyloxy-phenyl)-3-methyl-1-[4-(2-butyl-methylamino-1-yethoxy)-benzyl]-1H-indole

Mp = 101 - 104°C; ¹H NMR (DMSO) 7.45 (d, 4 H, J = 7.5 Hz), 7.40 - 7.25 (m, 8 H), 7.19 (d, 1 H, J = 8.8 Hz), 7.12-7.08 (m, 3 H), 6.80 (dd, 1 H, J = 6.5 Hz, J = 2.4 Hz), 6.72 (s, 4 H), 5.14 (s, 2 H), 5.13 (s, 2 H), 5.10 (s, 2 H), 3.91 (t, 2 H, J = 5.9 Hz), 2.64-2.59 (m, 2 H), 2.35-2.29 (m, 2 H), 2.17 (s, 3 H), 2.14 (s, 3 H), 1.40-1.31 (m, 2 H), 1.25-1.19 (m, 2 H), 0.83 (t, 3 H, 7.2 Hz); MS esl m/z 638 (M+).

Example No. 66a 5-Benzylxyloxy-2-(4-benzylxyloxy-phenyl)-3-methyl-1-[4-dimethylamino)-ethoxy]-benzyl]-1H-indole

Mp = 123-124°C

Example No. 67 5-Benzylxyloxy-2-(4-benzylxyloxy-phenyl)-3-methyl-1-[4-[2-(2-methyl-piperidin-1-yl)-ethoxy]-benzyl]-1H-indole

Mp = 121°C

Example No. 68 5-Benzylxyloxy-2-(4-benzylxyloxy-phenyl)-3-methyl-1-[4-[2-(3-methyl-piperidin-1-yl)-ethoxy]-benzyl]-1H-indole

Mp = 90°C

Example No. 69 5-Benzylxyloxy-2-(4-benzylxyloxy-phenyl)-3-methyl-1-[4-[2-(4-methyl-piperidin-1-yl)-ethoxy]-benzyl]-1H-indole

Mp = 98°C; ¹H NMR (DMSO) 7.46 (d, 4 H, J = 7.2 Hz), 7.42 - 7.36 (m, 4 H), 7.36-7.31 (m, 2 H), 7.28 (d, 2 H, J = 8.6 Hz), 7.19 (d, 1 H, J = 9.0 Hz), 7.12 - 7.10 (m, 3 H), 6.80 (dd, 1 H, J = 8.8 Hz, 2.4 Hz), 6.73 (s, 4 H), 5.15 (s, 2 H), 5.13 (s, 2 H), 5.11 (s, 2 H), 3.93 (t, 2 H, J = 5.9 Hz), 2.85 - 2.78 (m, 2 H), 2.62 - 2.56 (m, 2 H), 2.15 (s, 3 H), 1.97 - 1.87 (m, 2 H), 1.55 - 1.47 (m, 2 H), 1.30 - 1.20 (m, 1 H), 1.15 - 1.02 (m, 2 H), 0.85 (d, 3 H, J = 6.6 Hz); MS esl m/z 651 (M+).

Example No. 70 5-Benzylxyloxy-2-(4-benzylxyloxy-phenyl)-3-methyl-1-[4-[2-((cis)-2,6-Dimethyl-piperidin-1-yl)-ethoxy]-benzyl]-1H-indole

5 Mp = 106 - 107°C; ^1H NMR (DMSO) 7.46 (d, 4 H, J = 8.1 Hz), 7.42 - 7.36 (m, 4 H), 7.37 - 7.31 (m, 2 H), 7.29 (d, 2 H, J = 8.8 Hz), 7.18 (d, 1 H, J = 8.8 Hz), 7.14 - 7.09 (m, 3 H), 6.80 (dd, 1 H, J = 8.8 Hz, 2.4 Hz), 6.72 (s, 4 H), 5.14 (s, 2 H), 5.13 (s, 2 H), 5.11 (s, 2 H), 3.84 (t, 2 H, J = 7.0 Hz), 2.84 (t, 2 H, J = 6.6 Hz), 2.44 - 2.37 (m, 2 H), 2.15 (s, 3 H), 1.60 - 1.43 (m, 3 H), 1.32 - 1.18 (m, 1 H), 1.16 - 1.06 (m, 2 H), 1.01 (d, 6 H, J = 6.2 Hz).

Example No. 71 5-Benzylxyloxy-2-(4-benzylxyloxy-phenyl)-3-methyl-1-[4-[2-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-ethoxy]-benzyl]-1H-indole

10 Mp = 107°C; MS ESI m/z 705 (M+)+

Example No. 71a (1S,4R)-5-Benzylxyloxy-2-(4-benzylxyloxy-phenyl)-3-methyl-1-[4-[2-(2-Aza-bicyclo [2.2.1] hept-2-yl)-ethoxy]-benzyl]-1H-indole

15 The (1S,2R)-2-aza-bicyclo[2.2.1]heptane used to substitute the bromide was prepared according to the procedure outlined in Syn. Comm. 26(3), 577-584 (1996). Mp = 95 - 100°C; ^1H NMR (DMSO) 7.32 - 6.55 (m, 21 H), 5.10 - 4.90 (m, 6 H), 3.69 (t, 2 H, J = 5.9 Hz), 2.65 - 2.5 (m, 3 H), 2.10 (s, 2 H), 2.0 (s, 3 H), 1.50 - 1.0 (m, 7 H).

Example No. 72 5-Benzylxyloxy-2-(4-fluoro-phenyl)-3-methyl-1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-1H-indole

20 Oil; ^1H NMR (DMSO) 7.50 - 7.43 (m, 2 H), 7.42 - 7.33 (m, 4 H), 7.32 - 7.20 (m, 4 H), 7.13 (d, 1 H, J = 2.4 Hz), 6.83 (dd, 1 H, J = 2.4 Hz, 6.7 Hz), 6.71 (s, 4 H), 5.14 (s, 2 H), 5.11 (s, 2 H), 3.89 (t, 2 H, J = 5.9 Hz), 3.20 (m, 4 H), 2.74 (t, 2 H, J = 6.0 Hz), 2.15 (s, 3 H), 1.60 - 1.40 (m, 8 H); MS el m/z 562 (M+).

Example No. 72a 5-Benzylxyloxy-2-(4-fluoro-phenyl)-3-methyl-1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-1H-indole

25 Oil; ^1H NMR (DMSO) 7.32 - 6.53 (m, 16 H), 5.00 (s, 2 H), 4.96 (s, 2 H), 3.77 (t, 2 H, J = 5.8 Hz), 3.22 - 3.14 (m, 4 H), 2.40 (t, 2 H, J = 5.8 Hz), 2.0 (s, 3 H), 1.29-1.17 (m, 6 H).

Example No. 72b 5-Benzylxyloxy-2-(4-chloro-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole

30 Oil; ^1H NMR (DMSO) 7.52 (d, 2 H, J = 8.6 Hz), 7.46 (d, 2 H, J = 6.8 Hz), 7.41-7.37 (m, 4 H), 7.35 - 7.29 (m, 1 H), 7.25 (d, 1 H, J = 9.0 Hz), 7.14 (d, 1 H, J = 2.4 Hz), 6.83 (dd, 1 H, J = 8.8 Hz, 2.5 Hz), 6.72 - 6.65 (m, 4 H), 5.16 (s, 2 H), 5.11 (s, 2 H), 3.90 (t, 2 H, J = 5.9 Hz), 2.55 (t, 2 H, J = 6.0 Hz), 2.41 - 2.26 (m, 4 H), 2.16 (s, 3 H), 1.44 - 1.39 (m, 4 H), 1.38 - 1.29 (m, 2 H); MS el m/z 564 (M+).

Example No. 73 5-Benzylxyloxy-2-[3,4-methylenedioxy-phenyl]-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole

35 Foam; ^1H NMR (DMSO) 7.45 (d, 2 H, J = 7.0 Hz), 7.41-7.37 (m, 2 H), 7.33-7.29 (m, 1 H), 7.19 (d, 1 H, J = 8.8 Hz), 7.11 (d, 1 H, J = 2.2 Hz), 7.00 (d, 1 H, J = 7.9 Hz), 6.90 (d, 1 H, 1.4 Hz), 6.82 - 6.78 (m, 2 H), 6.74 (s, 4 H), 6.07 (s, 2 H), 5.16 (s, 2 H), 5.10 (s, 2 H), 3.93 (t, 2 H, J = 6.0 Hz), 2.56 (t, 2 H, J = 6.0 Hz), 2.41-2.35 (m, 4 H), 2.15 (s, 3 H), 1.48-1.41 (m, 4 H), 1.38-1.28 (m, 2 H); MS el m/z 574 (M+).

Example No. 74 5-Benzylxyloxy-2-[4-isopropoxy-phenyl]-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole

40 Foam; ^1H NMR (DMSO) 7.46 (d, 2 H, J = 7.7 Hz), 7.42 - 7.28 (m, 3 H), 7.25 (d, 2 H, J = 8.7 Hz), 7.17 (d, 1 H, J = 8.7 Hz), 7.11 (d, 1 H, J = 2.4 Hz), 6.99 (d, 2 H, J = 8.6 Hz), 6.79 (dd, 1 H, J = 2.4 Hz, 8.8 Hz), 6.73 (s, 4 H), 5.14 (s, 2 H), 5.10 (s, 2 H), 4.70 - 4.60 (m, 1 H), 3.92 (t, 2 H, J = 5.7 Hz), 2.55 (t, 2 H, 5.7 Hz), 2.40 - 2.30 (bs, 4 H), 2.15 (s, 3 H), 1.50 - 1.40 (m, 4 H), 1.40 - 1.30 (m, 2 H), 1.28 (d, 6 H, J = 6.2 Hz); MS el m/z 588 (M+).

Example No. 75 5-Benzylxyloxy-2-[4-methyl-phenyl]-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole

45 Oil; ^1H NMR (DMSO) 7.46 (d, 2 H, J = 7.2 Hz), 7.45 - 7.18 (m, 8 H), 7.12 (d, 1 H, J = 2.4 Hz), 6.81 (dd, 1 H, J = 2.4 Hz, 8.6 Hz), 6.73 (s, 4 H), 5.15 (s, 2 H), 5.10 (s, 2 H), 3.92 (t, 2 H, J = 5.9 Hz), 2.55 (t, 2 H, J = 5.9 Hz), 2.45 - 2.30

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(m, 7 H), 2.10 (s, 3 H), 1.50 - 1.40 (m, 4 H), 1.48 - 1.35 (m, 2 H); MS el m/z 544 (M+).

Example No. 77 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-5-benzyloxy-2-(3-benzyloxy-phenyl)-3-methyl-1H-indole

5 Mp = 103 - 105°C; ¹H NMR (DMSO) 7.47 - 7.45 (d, 2 H, J = 8.1 Hz), 7.41 - 7.35 (m, 7 H), 7.32 - 7.29 (t, 2 H, 7.0 Hz), 7.23 - 7.21 (d, 1 H, J = 8.7 Hz), 7.13 - 7.12 (d, 1 H, J = 2.1 Hz), 7.06 - 7.03 (m, 1 H), 6.95 - 6.91 (m, 2 H), 6.83 - 6.80 (m, 1 H), 6.75 - 6.73 (m, 4 H), 5.13 (s, 2 H), 5.11 (s, 2 H), 5.02 (s, 2 H), 3.90 - 3.87 (t, 2 H, J = 6.0 Hz), 2.76 - 2.73 (t, 2 H, J = 6.0 Hz), 2.49 - 2.48 (m, 4 H), 2.13 (s, 3 H), 1.51 (s, 8 H); IR 3400, 2900 cm⁻¹; MS el m/z 650 (M+); CHN calcd for C₄₄H₄₆N₂O₃.

10 **Example No. 78 5-Benzylxy-2-(4-benzyloxy-3-fluoro-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole**

15 Mp = 125-128°C; ¹H NMR (DMSO) 7.50 - 7.45 (m, 4 H), 7.43 - 7.28 (m, 7 H), 7.26-7.20 (m, 2 H), 7.14 - 7.09 (m, 2 H), 6.82 (dd, 1 H, J = 2.4 Hz, 8.8 Hz), 6.72 (s, 4 H), 5.21 (s, 2 H), 5.16 (s, 2 H), 5.11 (s, 2 H), 3.94 (t, 2 H, J = 5.8 Hz), 2.62 - 2.56 (m, 2 H), 2.41 - 2.36 (m, 4 H), 2.15 (s, 3 H), 1.45 - 1.40 (m, 4 H), 1.40 - 1.31 (m, 2 H); MS el m/Z 654 (M+); CHN calcd for C₄₃H₄₃FN₂O₃.

20 **Example No. 79 5-Benzylxy-2-(4-benzyloxy-3-fluoro-phenyl)-3-methyl-1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-1H-indole**

25 Mp = 122-124°C; ¹H NMR (DMSO) 7.50 - 7.28 (m, 10 H), 7.26 - 7.20 (m, 2 H), 7.15 - 7.10 (m, 2 H), 6.88 - 6.76 (m, 2 H), 6.70 (s, 4 H), 5.22 (s, 2H), 5.16 (s, 2H), 5.11 (s, 2H), 3.92 - 3.86 (m, 2H), 2.82 - 2.65 (m, 2H), 2.65 - 2.55 (m, 4H), 2.15 (s, 3H), 1.60 - 1.4 (m, 8H); MS el m/Z 668 (M+); CHN calcd for C₄₄H₄₅FN₂O₃.

30 **Example No. 80 5-Benzylxy-2-(3-methoxy-phenyl)-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-3-methyl-1H-indole**

35 Mp 86 - 87°C; ¹H NMR (DMSO) 7.50 - 7.49 (m, 2 H), 7.46 - 7.31 (m, 4 H), 7.24-7.21 (d, 1 H, J = 8.8 Hz), 7.15 - 7.14 (d, 1 H, J = 2.3 Hz), 7.00 - 6.93 (m, 2 H), 6.88 - 6.81 (m, 2 H), 6.75 (s, 4 H), 5.18 (s, 2 H), 5.12 (s, 2 H), 3.96 - 3.92 (t, 2 H, J = 5.9 Hz), 3.71 (s, 3 H), 2.59 - 2.55 (t, 2 H, J = 5.8 Hz), 2.37 (s, 4 H), 2.18 (s, 3 H), 1.49 - 1.42 (m, 4 H), 1.37 - 1.34 (m, 2 H); MS el m/z 561 (M+); CHN calcd for C₃₇H₄₀N₂O₃ + 0.25 H₂O.

40 **Example No. 81 5-Benzylxy-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-2-(4-trifluoromethoxy-phenyl)-1H-indole**

45 Mp = 107 - 108°C; ¹H NMR (DMSO) 7.52 - 7.45 (m, 6 H), 7.41 - 7.26 (m, 4 H), 7.17-7.16 (d, 1 H, J = 2.3 Hz), 6.87 - 6.84 (dd, 1 H, J = 2.3 Hz, J = 6.4 Hz), 6.75 - 6.68 (m, 4 H), 5.18 (s, 2 H), 5.13 (s, 2 H), 3.95 - 3.91 (t, 2 H, J = 5.9 Hz), 2.58 - 2.54 (t, 2 H, J = 5.9 Hz), 2.38 - 2.34 (m, 4 H), 2.17 - 2.15 (s, 3 H), 1.49 - 1.42 (m, 4 H), 1.35 - 1.34 (d, 2 H, J = 4.9 Hz); IR 3400, 2900, 1600 cm⁻¹; MS el m/z 615 (M+); CHN calcd for C₃₇H₃₇F₃N₂O₃.

50 **Example No. 82 (2-[4-[5-Benzylxy-2-(4-benzyloxy-phenyl)-3-methyl-indol-1-yl]methoxy]-ethoxy)-cyclohexyl-amine**

55 Mp = 87-90°C; ¹H NMR (DMSO) 7.46(dd, 4H, J= 6.9Hz, 0.6Hz), 7.42-7.27 (m, 9H), 7.19 (d, 1H, J= 9Hz), 7.14-7.08 (m, 3H), 6.80 (dd, 1H, J= 6.4Hz, 2.4Hz), 6.75- 6.70 (m, 4H), 5.15(s, 2H), 5.13 (s, 2H), 5.13(s, 2H), 3.89 (t, 2H, J= 5.6), 2.84 (m, 2H), 2.48 (m, 1H), 2.14 (s, 3H), 1.80(m, 2H), 1.65 (m, 2H), 1.61 (m, 1H), 0.96-1.19 (m, 5H); MS el m/Z 650 (M+); CHN calcd for C₄₄H₄₆N₂O₄.

55 **Example No. 83 5-Benzylxy-2-(4-benzyloxy-phenyl)-3-methyl-1-[4-methylpiperazin-1-yl]-ethoxy]-benzyl]-1H-indole**

55 Mp = 88-91°C; ¹H NMR (DMSO) 7.47 (m, 4H), 7.26-7.42 (m, 8H), 7.19 (d, 1H, J= 8.8), 7.10-1.12 (m, 3H), 6.80 (q, 1H, J= 6.3Hz, 2.4Hz), 6.73 (m, 4H), 5.15 (s, 2H), 5.13 (s, 2H), 5.11 (s, 2H), 3.94 (t, 2H, J= 5.9Hz), 2.59 (t, 2H), 2.42 (m, 4H), 2.29 (m, 4H), 2.15 (s, 3H), 2.12 (s, 3H); MS el m/Z 652 (M+); CHN calcd for C₄₃H₄₅N₃O₃.

55 **Example No. 84 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-5-benzyloxy-2-(3-methoxy-phenyl)-3-methyl-1H-indole**

Mp = 103 - 105°C; ¹H NMR (DMSO) 7.47 - 7.45 (d, 2 H, J = 8.1 Hz), 7.41 - 7.35 (m, 7 H), 7.32 - 7.29 (t, 2 H, 7.0

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Hz), 7.23 - 7.21 (d, 1 H, J = 8.7 Hz), 7.13 - 7.12 (d, 1 H, J = 2.1 Hz), 7.06 - 7.03 (m, 1 H), 6.95 - 6.91 (m, 2 H), 6.83 - 6.80 (m, 1 H), 6.75 - 6.73 (m, 4 H), 5.13 (s, 2 H), 5.11 (s, 2 H), 5.02 (s, 2 H), 3.90 - 3.87 (t, 2 H, J = 6.0 Hz), 2.76 - 2.73 (t, 2 H, J = 6.0 Hz), 2.49 - 2.48 (m, 4 H), 2.13 (s, 3 H), 1.51 (s, 8 H); IR 3400, 2900 cm⁻¹; MS el m/z 650 (M+); CHN calcd for C₄₄H₄₆N₂O₃.

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Data and procedures for compounds From Table 11 (ER Receptor Data Table, *infra*) of Text

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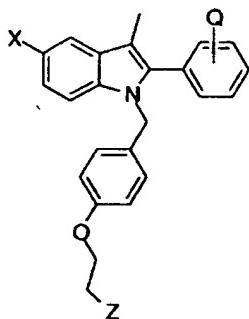


Table 7

No. 85	H	H	
No. 86	H	4'-OH	

Table 7 (Cont'd)

5	No. 87	OH	H
10	No. 88	OMe	4'-OH
15	No. 89	OH	4'-OMe
20	No. 90	OMe	4'-OMe
25	No. 91	OMe	4'-OMe
30	No. 92	OH	4'-OEt
35	No. 93	OH	4'-OEt
40	No. 94	F	4'-OH
45	No. 95	OH	H
50	No. 96	OH	4'-OH
55	No. 97	OH	4'-OH
	No. 98	OH	4'-OH

Table 7 (Cont'd)

5	No. 99	OH	4'-OH
10	No. 100	OH	4'-OH
15	No. 101	OH	4'-OH
20	No. 102	OH	4'-OH
25	No. 103	OH	4'-OH
30	No. 104	OH	4'-OH
35	No. 105	OH	4'-OH
40	No. 106	OH	4'-OH
45	No. 107	OH	4'-OH
50	No. 108	OH	4'-OH

The table lists nine compounds (No. 99 to No. 107) and one additional entry (No. 108). Each row contains three entries: a number, an OH group, and a 4'-OH group. To the right of each row is a chemical structure:

- No. 99: A seven-membered ring with an N atom at one corner.
- No. 100: A five-membered ring with an N atom at one corner.
- No. 101: A six-membered ring with an N atom at one corner.
- No. 102: A six-membered ring with an N atom at one corner and two methyl groups attached to the adjacent carbon.
- No. 103: A six-membered ring with an N atom at one corner and two ethyl groups attached to the adjacent carbon.
- No. 104: A six-membered ring with an N atom at one corner and two isopropyl groups attached to the adjacent carbon.
- No. 105: A six-membered ring with an N atom at one corner and a propyl group attached to the adjacent carbon.
- No. 106: A six-membered ring with an N atom at one corner and a quaternary ammonium cation (N^+) attached to the adjacent carbon.
- No. 107: A six-membered ring with an N atom at one corner and a cyclohexyl cation ($\text{C}_6\text{H}_{11}^+$) attached to the adjacent carbon.
- No. 108: A six-membered ring with an N atom at one corner and a cyclohexyl cation ($\text{C}_6\text{H}_{11}^+$) attached to the adjacent carbon.

Table 7 (Cont'd)

	No.	Substituent	Chemical Structure
5	No. 109	OH	4'-OH
10	No. 110	OH	4'-OH
15	No. 111	OH	4'-OH
20	No. 112	OH	4'-OH
25	No. 113	OH	4'-OH
30	No. 114	OH	4'-OH
35	No. 115	OH	4'-OH
40	No. 116	OH	4'-F
45	No. 117	OH	4'-F
50	No. 118	OH	3'-OMe,4'-OH
55	No. 119	OH	3',4'-OCH ₂ O-

Table 7 (Cont'd)

5	No. 120	OH	4'-O-iPr
10	No. 121	OH	4'-O-iPr
15	No. 122	OH	4'-O-Cp
20	No. 123	OH	4'-CF ₃
25	No. 124	OH	4'-CH ₃
30	No. 125	OH	4'-Cl
35	No. 126	OH	2',4',-Dimethoxy
40	No. 127	OH	3'-OH
45	No. 128	OH	3'-OH
50	No. 129	OH	4'-OH,3'-F
	No. 130	OH	4'-OH, 3'-F
	No. 131	OH	3'-OMe
	No. 132	OH	4'-OCF ₃

Hydrogenation of Indoles Containing Benzyl Ether(s) Method 7Illustrated For Example No. 972-(4-Hydroxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol

A suspension of 10% Pd/C (1.1 g) in EtOH was treated with a solution of No. 63 (2.2 g, 3.4 mmol) in THF/EtOH. Cyclohexadiene (6.0 mL, 63 mmol) was added and the reaction was stirred for 48 hours. The catalyst was filtered

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through Celite and the reaction mixture was concentrated and chromatographed on silica gel using a gradient elution of MeOH/CH₂Cl₂ (1:19 to 1:10) to yield 0.8 g of the product as a white solid. Mp = 109-113°C; CHN calc'd for C₂₉H₃₂N₂O₃ + 0.5 H₂O; ¹H NMR 9.64 (s, 1 H), 8.67 (s, 1 H), 7.14 (d, 2 H, J = 8.6 Hz), 7.05 (d, 1 H, J = 8.6 Hz), 6.84 (d, 2 H, J = 8.8 Hz), 6.79 (d, 1 H, J = 2.2 Hz), 6.74 (s, 4 H), 6.56 (dd, 1 H, J = 8.8, 2.4 Hz), 5.09 (s, 2 H), 3.95-3.93 (m, 2 H), 2.60-2.51 (m, 2 H), 2.39-2.38 (m, 4 H), 2.09 (s, 3 H), 1.46-1.45 (m, 4 H), 1.35-1.34 (m, 2 H); IR (KBr) 3350 (br), 2920, 1620, 1510 cm⁻¹; MS (EI) m/z 456.

Alternatively, the compounds may be dissolved in a THF/EtOH solution (or other appropriate solvent) and hydrogenated with H₂ and 10% Pd/C using either a ballon or Parr Hydrogenator. Either procedure is effective. In many of the examples, the compounds were made into acid addition salts. The procedure for the preparation of an HCl salt is given below (Method 8).

Method 8

1.0 g of Example No. 97 free base from the hydrogenation procedure above in a large test tube was dissolved in 20 mL of MeOH. This was treated with slow addition of 2.6 mL 1.0 N HCl and then 4.0 mL deionized water. The tube was partially opened to the atmosphere to encourage slow evaporation of the solvents. After about ten minutes, crystals began to appear and after 4 hours the solution was filtered and the solid crystals washed with water. The product was present as 0.42 g of white crystalline plates with a melting point of 184-185°C. The mother liquor yielded an additional crop of 0.30 g of white solid with a melting point of 177-182°C. CHN calc'd for C₂₉H₃₂N₂O₃ + HCl + 1 H₂O.

Alternatively, the compounds can be made into quaternary ammonium salts. An example procedure for the synthesis of example No. 107 is given below (Method 9).

Method 9

Example No. 107 2-(4-Hydroxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol methiodide

0.8 g of example No. 97 was dissolved in 18 mL THF and treated with 2 mL of methyl iodide. The solution was heated to reflux for an hour. The reaction was allowed to come to room temperature and the solids filtered to yield 0.72 g as a crystalline solid. Mp = 214 - 217°C, CHN calcd for C₂₉H₃₂N₂O₃ + CH₃I + 0.5 H₂O.

Example No. 106 2-(4-Hydroxy-phenyl)-3-methyl-1-[4-(2-dimethyl-1-yl-ethoxy)-benzyl]-1H-indol-5-ol methiodide

was prepared similarly to No. 106 except using No. 100 for starting material: Mp = 245 - 250°C; ¹H NMR (DMSO) 9.66 (s, 1 H), 8.69 (s, 1 H), 7.16 (d, 2 H, J = 8.4 Hz), 7.05 (d, 1 H, J = 8.8 Hz), 6.84 (d, 1 H, J = 8.6 Hz), 6.81 - 6.75 (m, 6 H), 6.56 (dd, 1 H, J = 2.4 Hz, 8.7 Hz), 5.12 (s, 2 H), 4.34 (m, 2 H), 3.70 (t, 2 H, J = 4.6 Hz), 3.11 (s, 9 H), 2.09 (s, 3 H); IR (KBr) 3250, 1500, 1250; MS el m/z 416 (M+); CHN calcd for C₂₆H₂₈N₂O₃ + 1.09 CH₃I + 0.8 H₂O.

Physical Data for final, deprotected compounds

The following compounds are either free bases, HCl salts or acetate salts. They were prepared according to the procedure outlined in method 7 using the appropriate benzyl ether for precursor. Where a compound from table 1 does not contain a free phenolic functionality, then it was unnecessary to debenzylate it and method 7 not applied. The physical data for these compounds (No. 85, No. 90- No. 91) is still presented below.

Example No. 85 4-[3-Methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole] (HCl)

Mp = 134 - 137°C; ¹H NMR (DMSO) 10.33 (s, 1 H), 7.56 - 7.38 (m, 6 H), 7.32 (d, 1 H, J = 8.1 Hz), 7.14 - 7.0 (m, 2 H), 6.80 (s, 4 H), 5.24 (s, 2 H), 4.28 (t, 2 H, J = 5.0 Hz), 3.50 - 3.40 (m, 4 H), 3.0 - 2.95 (m, 2 H), 2.10 (s, 3 H), 1.80 - 1.60 (m, 5 H), 1.40 - 1.35 (m, 1 H); IR 3400, 2900, 1510, 1250 cm⁻¹; MS (+) FAB m/z 425 [M+H]⁺; CHN calcd for C₂₉H₃₂N₂O + 1.0 HCl + 1.0 H₂O.

Example No. 86 4-[3-Methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-2-yl]-phenol hydrochloride (HCl)

Mp = 192 - 194°C; ¹H NMR (DMSO), 10.28 (s, 1 H), 9.75 (s, 1 H), 7.51 - 7.49 (m, 1 H), 7.27 (dd, 1 H, J = 7.0 Hz, 0.7 Hz), 7.18 (d, 2 H, J = 7.6 Hz), 7.09 - 7.02 (m, 2 H), 6.86 (d, 2 H, J = 8.6 Hz), 6.80 (s, 4 H), 5.20 (s, 2 H), 4.28 (t, 2 H, J = 4.9 Hz), 3.50 - 3.35 (m, 4 H), 3.0 - 2.85 (m, 2 H), 2.20 (s, 3 H), 1.80-1.60 (m, 5 H), 1.40 - 1.30 (m, 1 H); IR 3400,

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3100, 2600, 1500, 1225 cm⁻¹; MS el m/z 440 (M+); CHN calc for C₂₉H₃₂N₂O₂ + 1 HCl.

Example No. 87 3-Methyl-2-phenyl-1-[4-(2-piperidine-1-yl-ethoxy)-benzyl]-1H-indol-5-ol (HCl)

5 Mp = 228-230°C; ¹H NMR 10.1 (brs, 1 H), 8.76 (s, 1 H), 7.55 - 7.45 (m, 5 H), 7.10 (d, 1 H, J = 8.8 Hz), 6.85 - 6.80 (m, 5 H), 6.61 (d, 1 H, J = 8.8 Hz), 5.15 (s, 2 H), 4.25 (t, 2 H, J = 4.8 Hz), 3.47-3.35 (m, 4 H), 2.96-2.87 (m, 2 H), 2.12 (s, 3 H), 1.75-1.65 (m, 5 H), 1.31-1.28 (m, 1 H); MS el m/z 440 (M+); CHN calcd for C₂₉H₃₂N₂O₂ + 1 HCl + .33 H₂O; IR (KBr) 3200, 2500, 1450, 1200 cm⁻¹.

10 **Example No. 88 4-(5-Methoxy-3-methyl-1-[4-[2-(piperidin-1-yl)-ethoxy]-benzyl]-1H-indol-2-yl)-phenol**

Mpt = 87-90°C; ¹H NMR (DMSO) 9.67 (s, 1 H), 7.16 (d, 2 H, J = 8.6 Hz), 7.16 (1 H buried), 6.98 (d, 1 H, J = 2.4 Hz), 6.85 (d, 2 H, J = 8.6 Hz), 6.73 (s, 4 H), 6.69 (dd, 1 H, J = 8.8, 2.4 Hz), 5.13 (s, 2 H), 3.94 (t, 2 H, J = 5.7 Hz), 3.76 (s, 3 H), 2.63-2.50 (m, 2 H), 2.43-2.31 (m, 4 H), 2.15 (s, 3 H), 1.49-1.40 (m, 4 H), 1.39-1.25 (m, 2 H); IR (KBr) 3400 (br), 2920, 1610, 1520 cm⁻¹; MS el m/z 470; CHN calcd for C₃₀H₃₄N₂O₃ + 0.1 H₂O.

15 **Example No. 89 2-(4-methoxy-phenyl)-3-methyl-1-[4-[2-(piperidin-1-yl)-ethoxy]-benzyl]-1H-indol-5-ol**

20 Mp = 188-189°C; ¹H NMR (DMSO) 8.70 (s, 1 H), 7.27 (d, 2 H, J = 8.6 Hz), 7.06 (d, 1 H, J = 8.6 Hz), 7.02 (d, 2 H, J = 8.8 Hz), 6.81 (d, 1 H, J = 2.2 Hz), 6.73 (s, 4 H), 6.58 (dd, 1 H, J = 8.8, 2.4 Hz), 5.10 (s, 2 H), 3.93 (t, 2 H, J = 5.9 Hz), 3.79 (s, 3 H), 2.56 (t, 2 H, J = 5.9 Hz), 2.41-2.32 (m, 4 H), 2.10 (s, 3 H), 1.47-1.41 (m, 4 H), 1.34-1.31 (m, 2 H); MS el m/z 470; CHN calcd for C₃₀H₃₄N₂O₃ + 0.1 H₂O.

25 **Example No. 90 5-Methoxy-2-(4-methoxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole (HCl)**

30 Mp = 188-191°C; ¹H NMR (DMSO) 10.35 (brs, 1 H), 7.27 (d, 2 H, J = 8.8 Hz), 7.17 (d, 1 H, J = 8.8 Hz), 7.03 (d, 2 H, J = 8.6 Hz), 6.99 (d, 1 H, J = 2.5 Hz), 6.82-6.78 (m, 4 H), 6.71 (dd, 1 H, J = 8.8 Hz, J = 2.5 Hz), 5.17 (s, 2 H), 4.31 - 4.22 (m, 2 H), 3.79 (s, 3 H), 3.76 (s, 3 H), 3.43 - 3.36 (m, 4 H), 2.97 - 2.83 (m, 2 H), 2.16 (s, 3 H), 1.80 - 1.59 (m, 5 H), 1.41 - 1.26 (m, 1 H); IR (KBr) 2920, 1450, 1250 cm⁻¹; MS el m/z 484 (M+); CHN calc for C₃₁H₃₆N₂O₃ + 1 HCl.

35 **Example No. 91 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-5-methoxy-2-(4-methoxy-phenyl)-3-methyl-1H-indole (HCl)**

40 Mp = 161-163°C; ¹H NMR (DMSO) 10.65 (brs, 1 H), 7.27 (d, 2 H, J = 8.8 Hz), 7.17 (d, 1 H, J = 8.8 Hz), 7.03 (d, 2 H, J = 8.6 Hz), 6.99 (d, 1 H, J = 2.5 Hz), 6.82 - 6.77 (m, 4 H), 6.71 (dd, 1 H, J = 8.8 Hz, J = 2.5 Hz), 5.17 (s, 2 H), 4.27 (m, 2 H), 3.79 (s, 3 H), 3.76 (s, 3 H), 3.44 - 3.30 (m, 4 H), 3.17 (m, 2 H), 2.16 (s, 3 H), 1.82 - 1.77 (m, 4 H), 1.63 - 1.48 (m, 4 H); MS el m/z 499 (M+); CHN calc for C₃₂H₃₈N₂O₃ + 1 HCl.

45 **Example No. 92 2-(4-Ethoxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol**

Mp = 173-175°C; ¹H NMR (DMSO) 8.69 (s, 1 H), 7.25 (d, 2 H, J = 8.8 Hz), 7.04 (d, 1 H, J = 8.8 Hz), 6.99 (dd, 2 H, J = 6.8 Hz, J = 2.0 Hz), 6.80 (d, 1 H, J = 2.2 Hz), 6.73 (s, 4 H), 6.59 (dd, 1 H, J = 8.5 J = 2.2), 5.09 (s, 2 H), 4.05 (q, 2 H, J = 7.03 Hz), 3.93 (t, 2 H, J = 6.0 Hz), 2.62 - 2.56 (m, 2 H), 2.41 - 2.36 (m, 4 H), 2.09 (s, 3 H), 1.45 - 1.41 (m, 4 H), 1.38 - 1.30 (m, 5 H); MS el m/z 484 (M+); CHN calc for C₃₁H₃₆N₂O₃ + .25H₂O.

50 **Example No. 93 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-2-(4-ethoxy-phenyl)-3-methyl-1H-indol-5-ol**

55 Mp = 133-135°C; ¹H NMR (DMSO) 8.69 (s, 1 H), 7.25 (d, 2 H, J = 8.8 Hz), 7.04 (d, 1 H, J = 8.8 Hz), 6.99 (dd, 2 H, J = 6.8 Hz, J = 2.0 Hz), 6.80 (d, 1 H, J = 2.2 Hz), 6.73 (s, 4 H), 6.59 (dd, 1 H, J = 8.5 Hz, J = 2.2 Hz), 5.09 (s, 2 H), 4.05 (q, 2 H, J = 7.03 Hz), 3.90 (t, 2 H, J = 6.1 Hz), 2.75 (t, 2 H, J = 6.0 Hz), 2.62 - 2.58 (m, 4 H), 2.09 (s, 3 H), 1.58 - 1.44 (m, 8 H), 1.33 (t, 3 H, J = 7.0 Hz); IR (KBr) 2930, 1470, 1250 CM⁻¹; MS el m/z 498 (M+); CHN calc for C₃₂H₃₈N₂O₃.

Example No. 94 4-(5-Fluoro-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-2-yl)-phenol (HCl)

Mp = 223-225°C; ¹H NMR (DMSO) 10.30 (br s, 1 H), 7.27 - 7.23 (m, 2 H), 7.17 (d, 2 H, J = 8.6 Hz), 6.88 - 6.79

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(m, 7H), 5.20 (s, 2H), 4.28 (t, 2H, J = 5.0 Hz), 3.42 - 3.35 (m, 4 H), 3.00 - 2.85 (m, 2 H), 2.14 (s, 3 H), 1.78 - 1.70 (m, 4 H), 1.67 - 1.59 (m, 1 H), 1.40 - 1.26 (m, 1 H); MS el m/z 458 (M+).

Example No. 95 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-3-methyl-2-phenyl-1H-indol-5-ol (HCl)

Mp = 203-204°C; ¹H NMR (DMSO) 10.50 (brs, 1 H), 8.80 (s, 1 H), 7.50 - 7.38 (m, 5 H); 7.10 (d, 1 H, J = 8.8 Hz), 6.83 - 6.77 (m, 5 H), 6.60 (d, 1 H, J = 6.6 Hz), 5.15 (s, 2H), 4.26 (t, 2 H, J = 5.2 Hz), 3.45 - 3.35 (m, 4 H), 3.21-3.10 (m, 2 H), 2.12 (s, 3 H), 1.85-1.75 (m, 4 H), 1.70 - 1.51 (m, 4 H); MS el m/z 454 (M+); CHN calc for C₃₀H₃₄N₂O₂ + 1 HCl.

Example No. 96 2-(4-Hydroxy-phenyl)-3-methyl-1-[4-(2-pyrollidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol

Mp = 105-110°C; CHN calc'd for C₂₈H₃₀N₂O₃ + 0.4 H₂O; ¹H NMR (DMSO) 9.65 (s, 1 H), 8.67 (s, 1 H), 7.15 (d, 2 H, J = 8.6 Hz), 7.05 (d, 1 H, J = 8.6 Hz), 6.84 (d, 2 H, J = 2 H), 6.79 (d, 1 H, J = 2.4 Hz), 6.56 (dd, 1 H, J = 8.6, 2.2 Hz), 6.74 (s, 4 H), 5.09 (s, 2 H), 3.95 (t, 2 H, J = 5.7 Hz), 3.39-3.23 (m, 4 H), 2.80-2.75 (m, 2 H), 2.09 (s, 3 H), 1.67-1.64 (m, 4 H); IR (KBr) 3410 (br), 1620, 1510 cm⁻¹; MS (EI) m/z 442

Example No. 98 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol (HCl)

Mp = 168 - 171°C; ¹H NMR (DMSO) 10.11 (br s, 1 H), 9.70 (s, 1 H), 8.71 (s, 1 H); 7.15 (d, 2 H, J = 8.6 Hz), 7.05 (d, 1 H, J = 8.8 Hz), 6.85 (d, 2 H, J = 8.8 Hz), 6.80-6.77 (m, 5 H), 6.56 (dd, 1 H, J = 8.8 Hz, 2.2 Hz), 5.11 (s, 2 H), 4.26 (t, 2 H, J = 4.6 Hz), 3.48 - 3.30 (m, 4 H), 3.22 - 3.08 (m, 2 H), 2.09 (s, 3 H), 1.83 - 1.76 (m, 4 H), 1.67 - 1.48 (m, 4 H); IR (KBr) 3500 br, 3250 br, 2900, 1610; MS FAB m/z 471 (M+H+); CHN calcd for C₃₀H₃₄N₂O₃ + 2.5 H₂O + HCl.

Example No. 98 Acetate Salt

Made by the precipitation of No. 98 free base from acetone and acetic acid. Mp = 174 - 178°C

Example No. 99 1-[4-(2-Azocan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol

Mp = 98 - 102°C; ¹H NMR (DMSO) 9.63 (s, 1 H), 8.68 (s, 1 H), 7.15 - 7.13 (m, 2 H), 7.05 (d, 1 H, J = 8.5 Hz), 6.83 (dd, 2 H, J = 2.0 Hz, 6.6 Hz), 6.79 (d, 1 H, J = 2.2 Hz), 6.73 (s, 4 H), 6.55 (dd, 1 H, J = 2.2 Hz, 8.6 Hz), 5.08 (s, 2 H), 3.89 (t, 2 H, J = 5.7 Hz), 2.74 (t, 2 H, J = 5.4 Hz), 2.55 (bs, 4 H), 2.08 (s, 3 H), 1.55 (s, 2 H), 1.46 (s, 8 H); IR 3400, 2900, 1250 cm⁻¹; MS el m/z 484 (M+); CHN calcd for C₃₁H₃₆N₂O₃ + .30 H₂O.

Example No. 100 2-(4-Hydroxy-phenyl)-3-methyl-1-[4-(2-dimethyl-1-yl-ethoxy)-benzyl]-1H-indol-5-ol

Mp = 95 - 105°C; IR (KBr) 3400 br, 2900, 1610 cm⁻¹; MS el m/z 416 (M+); CHN calcd for C₂₆H₂₈N₂O₃ + 0.5 H₂O.

Example No. 101 2-(4-Hydroxy-phenyl)-3-methyl-1-[4-(2-diethyl-1-yl-ethoxy)-benzyl]-1H-indol-5-ol

Mp = 100-107°C; CHN calc'd for C₂₈H₃₂N₂O₃ + 0.25 H₂O; ¹H NMR (DMSO) 9.64 (s, 1 H), 8.67 (s, 1 H), 7.14 (d, 2 H, J = 8.6 Hz), 7.05 (d, 1 H, J = 8.8 Hz), 6.84 (d, 2 H, J = 8.6 Hz), 6.79 (d, 1 H, 2.2 Hz), 6.74 (s, 4 H), 6.56 (dd, 1 H, J = 8.8, 2.4 Hz), 5.09 (s, 2 H), 3.95-3.85 (m, 2 H), 2.80-2.60 (m, 2 H), 2.58-2.40 (m, 4 H), 2.09 (s, 3 H), 0.93 (t, 6 H, J = 7.0 Hz); IR (KBr) 3410 (br), 2950, 1610, 1510 cm⁻¹; MS FAB 445 (M+H+).

Example No. 102 1-[4-(2-Dipropylamino-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol

Mp = 83 - 86°C; ¹H NMR (DMSO) 9.64 (s, 1 H), 8.67 (s, 1 H), 7.14 (d, 2 H, J = 8.6), 7.04 (d, 1 H, J = 8.6 Hz), 6.83 (d, 2 H, J = 8.6 Hz), 6.78 (d, 1 H, J = 2.2 Hz), 6.72 (m, 4 H), 6.55 (dd, 1 H, J = 2.4 Hz, 8.2 Hz), 5.08 (s, 2 H), 3.88 (t, 2 H, J = 6.0 Hz), 2.80 - 2.63 (m, 2 H), 2.59 - 2.45 (m, 4 H), 2.10 (s, 3 H), 1.41 - 1.30 (m, 4 H), 0.79 (t, 6 H, J = 7.3 Hz); IR 3400, 2900, 1250; MS FAB m/z 473 [M+H+]; CHN calcd for C₃₀H₃₆N₂O₃ + .20 H₂O.

Example No. 103 1-[4-(2-Dibutylamino-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol

Foam; ¹H NMR (DMSO) 9.63 (s, 1 H), 8.66 (s, 1 H), 7.15 (d, 2 H, J = 8.6 Hz), 7.05 (d, 1 H, J = 8.8 Hz), 6.83 (d, 2 H, J = 8.6 Hz), 6.79 (d, 1 H, J = 4.2 Hz), 6.78 - 6.71 (m, 4 H), 6.55 (dd, 1 H, J = 8.6 Hz, J = 2.4 Hz), 5.10 (s, 2 H), 3.88 (t, 2 H, J = 5.5 Hz), 2.68-2.62 (m, 2H), 2.42-2.34 (m, 4 H), 2.08 (s, 3 H), 1.38 - 1.19 (m, 8H), 0.82 (t, 6 H, J = 7.2 Hz); IR (KBr) 3400, 1450 cm⁻¹; MS el m/z 501 (M+).

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Example No. 104 1-[4-(2-Diisopropylamino-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol

Mp = 96 - 102°C; ¹H NMR (DMSO) 9.64 (s, 1 H), 8.67 (s, 1 H), 7.14 (d, 2 H, J = 8.6 Hz), 7.04 (d, 1 H, J = 8.6 Hz), 6.83 (d, 2 H, J = 8.6 Hz), 6.79 (d, 1 H, J = 2.4 Hz), 6.77 - 6.69 (m, 4 H), 6.56 (dd, 1 H, J = 8.6 Hz, 2.2 Hz), 5.08 (s, 2 H), 3.75 (t, 2 H, J = 7.0 Hz), 3.01 - 2.92 (m, 2 H), 2.67 (t, 2 H, J = 7.0 Hz), 2.09 (s, 3 H), 0.93 (d, 12 H, 6.6 Hz); IR (KBr) 3400 br, 2940, 1620 cm⁻¹; MS FAB m/z 473 (M+H+); CHN calcd for C₃₀H₃₆N₂O₃ + 0.5 H₂O.

Example No. 105 1-[4-[2-(Butyl-methyl-amino)-ethoxy]-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol

Mp = 102-107°C; ¹H NMR (DMSO) 9.60 (s, 1 H), 8.67 (s, 1 H), 7.14 (d, 2 H, J = 8.4 Hz), 7.04 (d, 1 H, J = 8.6 Hz), 6.82 (d, 2 H, J = 8.8 Hz), 6.78 (d, 1 H, J = 2.3 Hz), 6.73 (s, 4 H), 6.55 (dd, 1 H, J = 8.8 Hz, J = 2.4 Hz), 5.08 (s, 2 H), 3.92 (t, 2 H, J = 6.0 Hz), 2.64-2.59 (m, 2 H), 2.38-2.29 (m, 2 H), 2.20 (br s, 3 H), 2.08 (s, 3 H), 1.40-1.31 (m, 2 H), 1.25-1.19 (m, 2 H), 0.83 (t, 3 H, 7.2 Hz); IR (KBr) 3420, 1460, 1230 cm⁻¹; MS el m/z 638 (M+).

Example No. 108 2-(4-Hydroxy-phenyl)-3-methyl-1-[4-[2-(2-methyl-piperidin-1-yl)-ethoxy]-benzyl]-1H-indol-5-ol

Mp = 121 - 123°C; ¹H NMR (DMSO) 9.65 (s, 1 H), 8.68 (s, 1 H), 7.14 (d, 2 H, J = 8.6 Hz), 7.04 (d, 1 H, J = 8.8 Hz), 6.84 (d, 2 H, J = 8.6 Hz), 6.79 (d, 1 H, J = 2.0 Hz), 6.74 (s, 4 H), 6.56 (dd, 1 H, J = 8.8 Hz, 2.4 Hz), 5.09 (s, 2 H), 3.97 - 3.86 (m, 2 H), 2.95 - 2.73 (m, 2 H), 2.62 - 2.53 (m, 1 H), 2.36 - 2.14 (m, 2 H), 2.09 (s, 3 H), 1.61 - 1.30 (m, 4 H), 1.28 - 1.09 (m, 2 H), 0.98 (d, 3 H, J = 5.1 Hz); IR (KBr) 3400, 2920, 2850, 1610 cm⁻¹; CHN calcd for C₃₀H₃₄N₂O₃ + 0.25 H₂O.

Example No. 109 2-(4-Hydroxy-phenyl)-3-methyl-1-[4-[2-(3-methyl-piperidin-1-yl)-ethoxy]-benzyl]-1H-indol-5-ol

Mp = 121 - 123°C; ¹H NMR (DMSO) 9.64 (s, 1 H), 8.67 (s, 1 H), 7.14 (dd, 2 H, J = 8.3 Hz, 1.4 Hz), 7.04 (dd, 1 H, J = 8.6 Hz, 1.2 Hz), 6.84 (dd, 2 H, J = 8.6 Hz, 1.7 Hz), 6.79 (s, 1 H), 6.79 (s, 4 H), 6.56 (d, 1 H, J = 8.6 Hz), 5.08 (s, 2 H), 3.94 (t, 2 H, J = 5.0 Hz), 2.86 - 2.71 (m, 2 H), 2.63 - 2.50 (m, 2 H), 2.48 (s, 3 H), 1.92 - 1.79 (m, 2 H), 1.63 - 1.35 (m, 5 H), 0.79 (d, 3 H, J = 5.2 Hz); IR (KBr) 3400, 2910, 1625 cm⁻¹; CHN calcd for C₃₀H₃₄N₂O₃ + 0.25 H₂O.

Example No. 110 2-(4-Hydroxy-phenyl)-3-methyl-1-[4-[2-(4-methyl-piperidin-1-yl)-ethoxy]-benzyl]-1H-indol-5-ol (HCl)

Mp = 154 - 162°C; ¹H NMR (DMSO) 10.00 (brs, 1 H), 9.71 (s, 1 H), 8.71 (s, 1 H), 7.15 (d, 2 H, J = 8.6 Hz), 7.05 (d, 1 H, J = 8.6 Hz), 6.85 (d, 2 H, J = 8.6 Hz), 6.83-6.77 (m, 4 H), 6.57 (dd, 1 H, J = 8.6 Hz, 2.2 Hz), 5.11 (s, 2 H), 4.27 (t, 2 H, J = 4.8 Hz), 3.51 - 3.35 (m, 4 H), 3.01 - 2.87 (m, 2 H), 2.09 (s, 3 H), 1.74 (d, 2 H, J = 13.4 Hz), 1.61 - 1.37 (m, 4 H), 0.88 (d, 3 H, J = 6.4 Hz); IR (KBr) 3410, 2910, 1620 cm⁻¹; MS el m/z 470 (M+H+); CHN calcd for C₃₀H₃₄N₂O₃ + HCl + 2 H₂O.

Example No. 111 1-[4-[2-(3,3-Dimethyl-piperidin-1-yl)-ethoxy]-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol

Mp = 100°C; ¹H NMR (DMSO) 9.65 (s, 1 H), 8.67 (s, 1 H), 7.15 (d, 2 H, J = 8.6 Hz), 7.05 (d, 1 H, J = 8.8 Hz), 6.84 (d, 2 H, J = 8.6 Hz), 6.79 (d, 1 H, J = 2.4 Hz), 6.74 (s, 4 H), 6.56 (dd, 1 H, J = 8.8, 2.4 Hz), 5.09 (s, 2 H), 3.93 (t, 2 H, J = 5.7 Hz), 2.60-2.50 (m, 2 H), 2.37-2.25 (m, 2 H), 2.09 (s, 3 H), 2.10-1.99 (m, 2 H), 1.46 (t, 2 H, J = 5.9 Hz), 1.13 (t, 2 H, J = 6.4 Hz), 0.86 (s, 6 H); MS el m/z 484.

Example No. 112 1-[4-[2-((cis)-2,6-Dimethyl-piperidin-1-yl)-ethoxy]-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol

Mp = 114 - 121°C; ¹H NMR (DMSO) 9.62 (s, 1 H), 8.64 (s, 1 H), 7.11 (d, 2 H, J = 8.6 Hz), 7.01 (d, 1 H, J = 8.6 Hz), 6.81 (d, 2 H, J = 8.8 Hz), 6.76 (d, 1 H, J = 2.2 Hz), 6.72 - 6.66 (m, 4 H), 6.53 (dd, 1 H, J = 8.6 Hz, 2.2 Hz), 5.06 (s, 2 H), 3.86 - 3.72 (m, 2 H), 2.86 - 2.76 (m, 2 H), 2.43 - 2.35 (m, 2 H), 2.06 (s, 3 H), 1.78 - 1.59 (m, 3 H), 1.29 - 1.17 (m, 1 H), 1.12 - 0.92 (m, 8 H); IR (KBr) 3400 br, 2920, 1630 cm⁻¹; MS FAB m/z 485 (M+H+); CHN calcd for C₃₁H₃₆N₂O₃ + 0.1 acetone + 0.75 H₂O.

Example No. 113 2-(4-Hydroxy-phenyl)-1-[4-[2-(4-hydroxy-piperidin-1-yl)-ethoxy]-benzyl]-3-methyl-1H-indol-5-ol

5 Mp = 80 - 90°C; ¹H NMR (DMSO) 9.66 (s, 1 H), 8.68 (s, 1 H), 7.15 (d, 2 H, J = 7.6 Hz), 7.04 (d, 1 H, J = 8.8 Hz),
 6.84 (dd, 2 H, J = 2.0 Hz, 6.6 Hz), 6.78 (d, 1 H, 2.2 Hz), 6.73 (s, 4 H), 6.55 (dd, 1 H, J = 2.2 Hz, 8.6 Hz), 5.09 (s, 2 H),
 4.50 (d, 1 H, J = 4.2 Hz), 3.92 (t, 2 H, J = 5.8 Hz), 3.40 (m, 2 H), 2.72 (m, 2 H), 2.60 (m, 2 H), 2.10 (s, 3 H), 2.15-2.05
 (m, 1 H), 1.75-1.63 (m, 2 H), 1.42-1.28 (m, 2 H); IR (KBr) 3400, 2900, 1250 cm⁻¹; MS el m/z 472 (M+); CHN calcd for
 $C_{29}H_{32}N_2O_4 + .11CH_2Cl_2$.

10 Example No. 114 (1S,4R)-1-[4-[2-(2-Aza-bicyclo [2.2.1] hept-2-yl)-ethoxy]-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol

15 Mp = 125 - 130°C; ¹H NMR (DMSO) 9.65 (s, 1 H), 8.67 (s, 1 H), 7.13 (d, 2 H, J = 8.6 Hz), 7.04 (d, 1 H, J = 8.5
 Hz), 6.83 (dd, 2 H, J = 2.0 Hz, 6.6 Hz), 6.78 (d, 1 H, J = 2.2 Hz), 6.73 (s, 4 H), 6.55 (dd, 1 H, J = 2.2 Hz, 8.6 Hz), 5.08
 (s, 2 H), 3.95 - 3.8 (m, 2 H), 2.90 - 2.70 (3 H), 2.30 - 2.20 (m, 2 H), 2.10 (s, 3 H), 1.70 - 1.60 (m, 1 H), 1.60 - 1.30 (m,
 4 H), 1.25 - 1.15 (m, 2 H); IR (KBr) 3400, 2950, 1500; MS (+) FAB m/z 469 [M+H]⁺; CHN calcd for $C_{30}H_{32}N_2O_3 + .34$
 EtOAc.

20 Example No. 115 2-(4-Hydroxy-phenyl)-3-methyl-1-[4-[2-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-ethoxy]-benzyl]-1H-indol-5-ol

25 Mp = 98 - 100°C; ¹H NMR (DMSO) 9.64 (s, 1 H), 8.67 (s, 1 H), 7.14 (d, 2 H, J = 8.6 Hz), 7.05 (d, 1 H, J = 8.6 Hz),
 6.84 (d, 2 H, J = 8.6 Hz), 6.79 (d, 1 H, J = 2.4 Hz), 6.75 - 6.69 (m, 4 H), 6.56 (dd, 1 H, J = 8.6 Hz, 2.4 Hz), 5.08 (s, 2
 H), 3.83 (t, 2 H, J = 5.9 Hz), 3.12 - 3.07 (m, 1 H), 2.94 - 2.87 (m, 1 H), 2.85 (d, 1 H, J = 9.2 Hz), 2.78 - 2.70 (m, 1 H),
 2.17 (d, 1 H, J = 9.2 Hz), 2.09 (s, 3 H), 1.55-1.42 (m, 2 H), 1.29 (q, 2 H, J = 13.6 Hz), 1.14 (s, 3 H), 1.11 - 1.02 (m, 2
 H), 0.96 (s, 3 H), 0.82 (s, 3 H); IR (KBr) 3400 br, 2940, 2900, 1630 cm⁻¹; MS ESI m/z 525 (M+H⁺); CHN calcd for
 $C_{34}H_{40}N_2O_3 + 0.5 H_2O$.

30 Example No. 116 2-(4-Fluoro-phenyl)-3-methyl-1-[4-(2-piperidine-1-yl-ethoxy)-benzyl]-1H-Indol-5-ol (HCl)

35 Mp = 201 - 203°C; ¹H NMR (DMSO) 10.22 (s, 1 H), 8.78 (s, 1 H), 7.45 - 7.35 (m, 2 H), 7.34 - 7.25 (m, 2 H), 7.11
 (d, 1 H, J = 8.6 Hz), 6.90 - 6.70 (m, 5 H), 6.61 (dd, 1 H, J = 2.4 Hz, 8.8 Hz), 5.15 (s, 2 H), 4.27 (t, 2 H, 4.8 Hz), 3.50 -
 3.34 (m, 4 H), 3.0 - 2.85 (m, 2 H), 2.10 (s, 3 H), 1.80 (m, 5 H), 1.40 - 1.25 (m, 1 H); MS el m/z 458 (M+); CHN calcd for
 $C_{29}H_{31}FN_2O_2 + 1 HCl$.

35 Example No. 117 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-2-(4-fluorophenyl)-3-methyl-1H-Indol-5-ol

40 Mp = 181 - 184°C; ¹H NMR (DMSO) 10.68 (s, 1 H), 8.80 (s, 1 H), 7.50 - 7.36 (m, 2 H), 7.34 - 7.26 (m, 2 H), 7.12
 (d, 1 H, J = 8.8 Hz), 6.86 - 6.73 (m, 5 H), 6.63 (dd, 1 H, J = 2.2 Hz, 8.5 Hz), 5.13 (s, 2 H), 4.29 (t, 2 H, J = 5.2 Hz), 3.50
 - 3.30 (m, 4 H), 3.20 - 3.08 (m, 2 H), 2.11 (s, 3 H), 1.90 - 1.70 (m, 4 H), 1.68 - 1.45 (m, 4 H); IR (KBr) 3500, 3100, 2910,
 1450, 1250 cm⁻¹; MS el m/z 472 (M+); CHN calcd for $C_{30}H_{33}FN_2O_2 + 1 HCl$.

45 Example No. 118 2-(3-Methoxy-4-hydroxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol (HCl)

50 Mp = 161-163°C ; ¹H NMR (DMSO) 10.12 (brs, 1 H), 9.25 (s, 1 H), 8.71 (s, 1 H), 7.05 (d, 1 H, J = 8.5Hz), 6.85 -
 6.79 (m, 8 H), 6.57 (dd, 1 H, J = 8.5Hz, J = 2.2Hz), 5.13 (s, 2 H), 4.27 (t, 2 H, J = 5.0Hz), 3.64 (s, 3 H), 3.44 - 3.37
 (m, 4 H), 2.93-2.85 (m, 2 H), 2.11 (s, 3 H), 1.80 - 1.60 (m, 5 H), 1.40 - 1.25 (m, 1 H); MS el m/z 486 (M+); CHN calc for
 $C_{30}H_{34}N_2O_4 + 1HCl + 1H_2O$; IR (KBr) 3190, 1470, 1230 cm⁻¹.

50 Example No. 119 2-Benzo[1,3]dioxol-5-yl-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-Indol-5-ol (HCl)

55 Mp = 122-125°C ; ¹H NMR (DMSO) 9.80 (brs , 1 H), 8.73 (s , 1 H), 7.07 (d , 1 H, J = 8.7 Hz), 7.02 (d , 1 H, J = 8.0
 Hz) , 6.89 (d , 1 H,J = 1.7 Hz), 6.80-6.75 (m , 6 H), 6.58 (dd , 1 H , J = 6.4 Hz, J = 2.2Hz), 6.06 (s , 2H), 5.13 (s , 2H),
 4.30 - 4.19 (m , 2 H), 3.51 - 3.30 (m , 4 H), 2.99-2.85 (m , 2 H), 2.10 (s , 3 H), 1.81-1.59 (m , 5 H), 1.41-1.26 (m , 1 H);
 MS el m/z 484(M+); CHN calc for $C_{30}H_{12}N_2O_4 + HCl + .26 H_2O$.

Example No. 120 2-(4-Isopropoxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol (HCl)

Mp = 120 - 125°C; ¹H NMR (DMSO) 10.18 (s, 1 H), 8.73 (s, 1 H), 7.25 (d, 2 H, J = 8.6 Hz), 7.04 (d, 1 H, J = 8.8 Hz), 6.99 (d, 2 H, J = 8.8 Hz), 6.82 - 6.80 (m, 5 H), 6.59 (dd, 1 H, J = 2.2 Hz, 8.6 Hz), 5.12 (s, 2 H), 4.67 - 4.61 (m, 1 H), 4.27 (t, 2 H, J = 4.8 Hz), 3.50 - 3.35 (m, 4 H), 3.0 - 2.85 (m, 2 H), 2.10 (s, 3 H), 1.80 - 1.60 (m, 5 H), 1.40 - 1.25 (m, 7 H); IR (KBr) 3400, 3000, 1500, 1250; MS el m/z 498 (M+); CHN calcd for C₃₂H₃₈N₂O₃ + 1.0 HCl + .70 H₂O.

Example No. 121 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-2-(4-isopropoxypyhenyl)-3-methyl-1H-indol-5-ol (HCl)

Mp = 120 - 125°C; ¹H NMR (DMSO) 10.36 (s, 1 H), 8.73 (s, 1 H), 7.26 - 7.23 (m, 2 H), 7.05 (d, 1 H, J = 8.8 Hz), 7.01 - 6.98 (m, 2 H), 6.85 - 6.75 (m, 5 H), 6.57 (dd, 1 H, J = 2.2 Hz, 8.6 Hz), 5.12 (s, 2 H), 4.67 - 4.61 (m, 1 H), 4.27 (t, 2 H, J = 4.8 Hz), 3.50 - 3.30 (m, 4 H), 3.20 - 3.10 (m, 2 H), 2.10 (s, 3 H), 1.85-1.75 (m, 4 H), 1.65 - 1.50 (m, 4 H), 1.27 (d, 6 H, J = 6.1 Hz); IR (KBr) 3400, 1500, 1250; MS el m/z 512 (M+); Calcd for C₃₃H₄₀N₂O₃ + 1.0 HCl + .5 H₂O.

Example No. 122 2-(4-Cyclopenyloxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol

Mp = 121 - 135°C; ¹H NMR (DMSO) 9.80 (br s, 1 H), 8.72 (s, 1 H), 7.24 (d, 2 H, J = 8.8 Hz), 7.05 (d, 1 H, J = 8.8 Hz), 6.98 (d, 2 H, J = 8.8 Hz), 6.83 - 6.78 (m, 5 H), 6.57 (dd, 1 H, J = 8.8 Hz, 2.4 Hz), 5.13 (s, 2 H), 4.86 - 4.82 (m, 1 H), 4.25 (t, 2 H, J = 4.8 Hz), 3.50 - 3.38 (m, 4 H), 2.92 (q, 2 H, J = 8.8 Hz), 2.11 (s, 3 H), 1.98 - 1.85 (m, 2 H), 1.81 - 1.56 (m, 11 H), 1.41 - 1.29 (m, 1 H); IR (KBr) 3400, 2920, 1620 cm⁻¹; MS el m/z 524 (M+); CHN calcd for C₃₄H₄₀N₂O₃ + 0.5 H₂O.

Example No. 123 3-Methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-2-(4-trifluoromethyl-phenyl)-1H-indol-5-ol

Mp = 174°C; ¹H NMR (DMSO) 8.8 (s, 1 H), 7.82 (d, 2 H, J = 8.1 Hz), 7.59 (d, 2 H, J = 7.9 Hz), 7.17 (d, 1 H, J = 8.6 Hz), 6.86 (d, 1 H, J = 2.4 Hz), 6.75 - 6.68 (m, 4 H), 6.65 (dd, 1 H, J = 8.8 Hz, 2.4 Hz), 5.16 (s, 2 H), 3.93 (t, 2 H, J = 5.7 Hz), 2.62-2.56 (m, 2 H), 2.42 - 2.32 (m, 4 H), 2.15 (s, 3 H), 1.48 - 1.40 (m, 4 H), 1.39 - 1.29 (m, 2 H); IR (KBr) 3410, 2910, 2850, 1620 cm⁻¹; MS el m/z 508 (M+); CHN calcd for C₃₀H₃₁F₃N₂O₂ + 0.25 H₂O.

Example No. 124 3-Methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-2-p-tolyl-1H-indol-5-ol

Mp = 162 - 164°C; ¹H NMR (DMSO) 8.70 (s, 1 H), 7.28 - 7.24 (m, 4 H), 7.07 (d, 1 H, J = 8.4 Hz), 6.81 (d, 1 H, J = 2.2 Hz), 6.73 (s, 4 H), 6.58 (dd, 1 H, J = 2.4 Hz, 8.8 Hz), 5.11 (s, 2 H), 3.92 (t, 2 H, J = 5.9 Hz), 2.55 (t, 2 H, J = 5.9 Hz), 2.45 - 2.30 (m, 7 H), 2.10 (s, 3 H), 1.50 - 1.40 (m, 4 H), 1.48 - 1.35 (m, 2 H); IR (KBr) 3400, 2900, 1200; MS el m/z 454 (M+); CHN calcd for C₃₀H₃₄N₂O₂.

Example No. 125 2-(4-Chloro-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-Indol-5-ol (HCl)

Mp = 161-164°C; ¹H NMR (DMSO) 10.12 (brs, 1 H), 8.80 (s, 1 H), 7.53 (d, 2 H, J = 8.3 Hz), 7.36 (d, 2 H, J = 8.8 Hz), 7.12 (d, 1 H, J = 8.8 Hz), 6.85-6.75 (m, 5 H), 6.63 (dd, 1 H, J = 8.8 Hz, 2.4 Hz), 5.14 (s, 2 H), 4.29-4.22 (m, 2 H), 3.45-3.36 (m, 4 H), 2.97 - 2.84 (m, 2 H), 2.11 (s, 3 H), 1.83 - 1.61 (m, 5 H), 1.37 - 1.25 (m, 1 H); MS el m/z 475 (M+); CHN calc for C₂₉H₃₁ClN₂O₂ + HCl + .25 H₂O.

Example No. 126 2-(2,4-Dimethoxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol

Mp = 85 - 92°C; ¹H NMR (DMSO) 8.62 (s, 1 H), 7.10 (d, 1 H, J = 8.4 Hz), 7.01 (d, 1 H, J = 8.6 Hz), 6.80 - 6.70 (m, 5 H), 6.69 (d, 1 H, 2.2 Hz), 6.59 (dd, 1 H, J = 2.4 Hz, 8.5 Hz), 6.52 (dd, 1 H, J = 2.4 Hz, 8.8 Hz), 5.02 (d, 1 H, J = 6.5 Hz), 4.83 (d, 1 H, J = 6.3 Hz), 4.0 - 3.90 (m, 2 H), 3.80 (s, 3 H), 3.67 (s, 3 H), 2.65 - 2.50 (m, 2 H), 2.45 - 2.30 (m, 4 H), 2.0 (s, 3 H), 1.55 - 1.40 (m, 4 H), 1.39 - 1.30 (m, 2 H); IR (KBr) 3400, 2900, 1520, 1250; MS el m/z 500 (M+); CHN calcd for C₃₁H₃₆N₂O₄ + 0.05 CH₂Cl₂.

Example No. 127 2-(3-Hydroxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol

Mp = 115 - 118°C; ¹H NMR (DMSO) 9.57 (s, 1 H), 8.71 (s, 1 H), 7.27 - 7.23 (t, 1 H, J = 8.1 Hz), 7.06 - 7.04 (d, 1 H, J = 8.8 Hz), 6.81 - 6.74 (m, 8 H), 6.59 - 6.56 (dd, 1 H, J = 2.3 Hz, J = 6.3 Hz), 5.12 (s, 2 H), 3.94 - 3.91 (t, 2 H, J = 5.9 Hz), 2.57 - 2.54 (t, 2 H, J = 5.8 Hz), 2.36 (s, 4 H), 2.11 (s, 3 H), 1.45 - 1.41 (m, 4 H), 1.34 - 1.33 (m, 2 H); IR (KBr) 3400, 2900 cm⁻¹; MS el m/z 456 (M+); CHN calcd for C₂₉H₃₂N₂O₃ + 1.0 H₂O.

Example No. 128 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-2-(3-hydroxyphenyl)-3-methyl-1H-indole-5-ol

5 Mp = 94 - 97°C; ^1H NMR (DMSO) 9.58 (s, 1 H), 8.71 (s, 1 H), 7.27 - 7.23 (t, 1 H, J = 7.9 Hz), 7.07 - 7.04 (d, 1 H, J = 8.7 Hz), 6.81 - 6.74 (m, 8 H), 6.59 - 6.56 (dd, 1 H, J = 2.4 Hz, J = 6.3 Hz), 5.12 (s, 2 H), 3.9 (m, 2 H), 2.80 (s, 2 H), 2.65 (s, 4 H), 2.11 (s, 3 H), 1.54 - 1.50 (m, 8 H); IR 3400, 2900 cm^{-1} ; MS el m/z 470 (M+); CHN calcd for $\text{C}_{30}\text{H}_{34}\text{N}_2\text{O}_3$ + 0.75 H_2O + 0.23 Ethyl Acetate.

Example No. 129 2-(3-Fluoro-4-hydroxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol

10 Mp = 117-119°C; ^1H NMR (DMSO) 10.1 (s, 1H), 8.71 (s, 1H), 7.10 - 6.95 (m, 4H), 6.80 (d, 1H, J = 2.2Hz), 6.74 (s, 4H), 6.59 (dd, 1H, J = 2.2 Hz, 8.5 Hz), 5.1 (s, 2H), 3.93 (t, 2H, J = 5.9 Hz), 2.56 (t, 2H, J = 5.8 Hz), 2.44 - 2.30 (m, 4H), 2.10 (s, 3H), 1.45 - 1.40 (m, 4H), 1.36 - 1.32 (m, 2H); MS el m/z 475 (M+); CHN calcd for $\text{C}_{29}\text{H}_{31}\text{FN}_2\text{O}_3$.

Example No. 130 2-(3-Fluoro-4-hydroxy-phenyl)-3-methyl-1-[4-(azepan-1-yl-ethoxy)-benzyl]-1H-indol-5-ol

15 Mp = 88 - 91°C; ^1H NMR (DMSO) 10.10 (s, 1H), 8.71 (s, 1H), 7.12 - 6.94 (m, 4H), 6.80 (d, 1H, J = 2.2 Hz), 6.74 (s, 4H), 6.58 (dd, 1H, J = 2.2 Hz, 8.5 Hz), 5.10 (s, 2H), 3.91 (t, 2H, J = 5.9 Hz), 2.76 (t, 2H, J = 5.9), 2.62 - 2.60 (m, 4H), 2.10 (s, 3H), 1.70 - 1.40 (m, 8H); MS el m/z 488 (M+); CHN calcd for $\text{C}_{30}\text{H}_{33}\text{FN}_2\text{O}_3$.

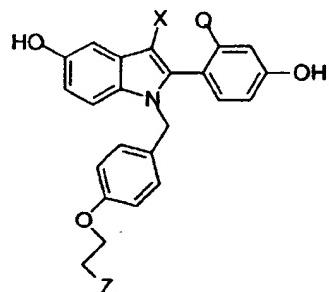
Example No. 131 2-(3-Methoxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol

20 Mp = 120 - 123°C; ^1H NMR (DMSO) 8.76 (s, 1H), 7.42 - 7.46 (t, 1H, J = 7.9 Hz), 7.12 - 7.09 (d, 1H, J = 8.7 Hz), 6.99 - 6.92 (m, 2H), 6.86 - 6.83 (m, 2H), 6.76 (s, 4H), 6.63 - 6.60 (dd, 1H, J = 2.1 Hz, J = 6.5 Hz), 5.14 (s, 2H), 3.96 - 3.92 (t, 2H, J = 5.9 Hz), 3.70 (s, 3H), 2.59 - 2.55 (t, 2H, J = 5.9 Hz), 2.37 (s, 4H), 2.14 (s, 3H), 1.49 - 1.44 (m, 4H), 1.35 - 1.34 (m, 2H); IR 3400, 2950, 1600 cm^{-1} ; MS el m/z 471 (M+); CHN calcd for $\text{C}_{30}\text{H}_{34}\text{N}_2\text{O}_3$.

Example No. 132 3-Methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-2-(4-trifluoromethoxy-phenyl)-1H-indole-5-ol

30 Mp = 122 - 125°C; ^1H NMR (DMSO) 8.80 (s, 1H), 7.51 - 7.45 (m, 4H), 7.17 - 7.14 (d, 1H, J = 8.7 Hz), 6.85 - 6.84 (d, 1H, J = 2.0 Hz), 6.75 - 6.69 (m, 4H), 6.66-6.62 (m, 1H), 5.14 (s, 2H), 3.95 - 3.92 (t, 2H, J = 5.8 Hz), 2.59 - 2.55 (t, 2H, J = 5.6 Hz), 2.49 - 2.38 (m, 4H), 2.13 (s, 3H), 1.47 - 1.44 (m, 4H), 1.36 - 1.34 (d, 2H, J = 4.8 Hz); IR 3400, 2900, 1600 cm^{-1} ; MS el m/z 525 (M+); CHN calcd for $\text{C}_{30}\text{H}_{31}\text{F}_3\text{N}_2\text{O}_3$ + 0.25 H_2O .

35 Synthetic procedures and physical data for compounds substituted with chloro, ethyl or cyano groups at the 3-position of the indole



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Table 8

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No.	Substituent	Substituent	Structure
No. 133	Cl	H	N
No. 134	Cl	H	N
No. 135	Cl	H	N
No. 136	Cl	CH ₃	N
No. 137	Et	H	N
No. 138	CN	H	N
No. 139	CN	H	N

Synthesis of 3-chloro analogues No. 133- No. 136

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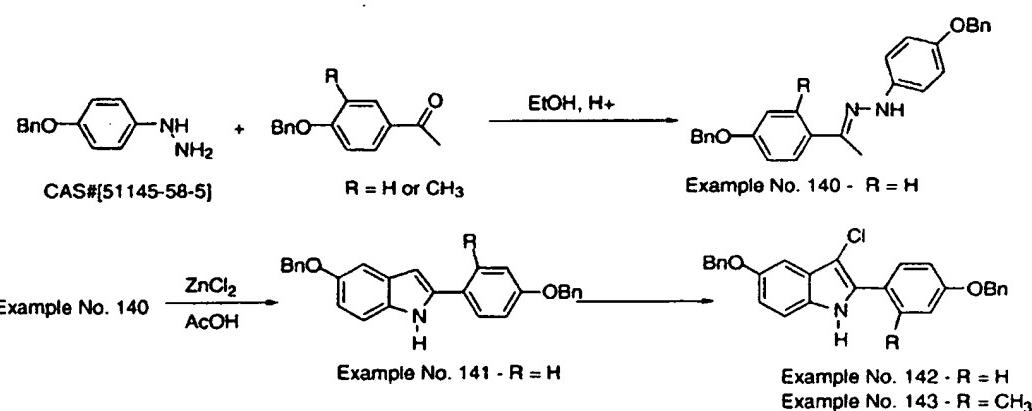
Scheme 14**Synthesis of 3-chloroindole**

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**Example No. 140 Formation of hydrazone**

4-Benzylxophenylhydrazine CAS No. [51145-58-5] (50.0 g, 233.4 mmol) was mixed with 4-benzylxoyacetophenone

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none CAS No. [54696-05-8] (63.0 g, 280.0 mmol) in pure ethanol (800 mL). A catalytic amount of acetic acid (5 drops) was added. The reaction was heated to reflux for 2.5 hrs. During the course of refluxing, the condensed product solidified out of the hot solution. The reaction was cooled down to rt. The desired product was collected by vacuum filtration as a light yellow solid (85 g, 86%). Mp = 165-174°C; ¹H NMR (DMSO) 8.91 (s, 1 H), 7.68 (d, 2 H, J = 8.8 Hz), 7.48 - 7.32 (m, 10 H), 7.12 (d, 2 H, J = 9 Hz), 7.00 (d, 2 H, J = 8.8 Hz), 6.88 (d, 2 H, J = 9.0 Hz). 5.11 (s, 2 H), 5.01 (s, 2 H), 2.17 (s, 3 H); MS el m/z 422 (M+).

Example No. 141 Formation of indole from hydrazone: 5-Benzylxy-2-(4-benzylxy-phenyl)-1H-indole

A flask was charged with N-(4-Benzylxy-phenyl)-N'-(1-(4-benzylxy-phenyl)-ethylidene)-hydrazine (No. 140) (10.0 g, 23.7 mmol), ZnCl₂ (8.06 g, 59.17 mmol), acetic acid (70 mL). The reaction flask was heated to 105 °C for no more than 20 min. During the heating period, the reaction was monitored carefully by TLC for the disappearance of the starting material. The progress of the reaction could be shown as the product solidified out of the solution while heating. The reaction was then cooled to rt and more product crashed out was observed. The reaction content was poured into a separatory funnel containing ether (100 mL) and H₂O (200 mL), which was shaken vigorously. The insoluble residue as the desired product stayed in the ether layer which was collected by vacuum filtration. The product was further purified by trituration in ether to give a light gray solid (4.4 g, 46%). Mp = 202 - 204°C; ¹H NMR (DMSO) 11.24 (s, 1 H), 7.73 (d, 2 H, J = 8.8 Hz), 7.48-7.41 (m, 4 H), 7.45 - 7.27 (m, 6 H), 7.25 (d, 1 H, J = 8.6 Hz), 7.12 - 7.04 (m, 3 H), 6.77 (dd, 1 H, J = 2.4 Hz, 8.6 Hz), 6.65 (d, 1 H, J = 1.5 Hz), 5.14 (s, 2 H), 5.08 (s, 2 H); IR 3420, 3000, 1625 cm⁻¹; MS el m/z 405 (M+); CHN calcd for C₂₈H₂₃NO₂ + 0.40 H₂O.

Example No. 142 Chlorination of Indole to render 5-Benzylxy-3-chloro-2-(4-benzylxy-phenyl)-1H-indole

A flask was charged with 5-Benzylxy-2-(4-benzylxy-phenyl)-1H-indole No. 141 (8.0 g, 20.0 mmole) and CH₂Cl₂ (50mL). The reaction was cooled to 0°C and n-chlorosuccinimide(2.9g, 22mmole) was added . The reaction was stirred at 0°C for 20min. The reaction was then washed with 10% sodium sulfite solution,dried over MgSO₄, and concentrated. To the resulting brown solid was added MeOH and the mixture was stirred for 15 min. The solid was filtered to give 6.8g of a tan solid (78%). Mp = 157-160°C ; ¹H NMR (DMSO) 11.5 (s , 1 H), 7.80 (d , 2 H , J = 7.0 Hz), 7.42-7.28 (m, 11 H), 7.17 (d, 2 H , J = 8.7 Hz), 7.01 (d, 1 H , J = 2.2Hz), 6.88 (dd , 1 H, J = 8.8 Hz, J = 2.4 Hz), 5.17 (s , 2H), 5.13 (s , 2H); MS el m/z 439 (M+).

Example No. 143 5-Benzylxy-3-chloro-2-(2-methyl-4-benzylxy-phenyl)-1H-indole

This indole synthesized analogously to indole No. 142 immediately preceding: Mp = ¹H NMR (DMSO) 11.34 (s , 1 H), 7.48 - 7.44 (m, 4 H), 7.42 - 7.24 (m , 8 H), 7.02 (dd , 2 H , J = 9.3 Hz , J = 2.4 Hz), 6.95 (dd , 1 H , J = 8.4 Hz , J = 2.6Hz), 6.88 (dd , 1 H, J = 8.8Hz, J =2.4 Hz), 5.16 (s , 2 H), 5.14 (s , 2 H), 2.23 (s , 3 H); MS el m/z 453 (M+).

Example No. 144 Alkylation of indole to give {4-[5-Benzylxy-2-(4-benzylxy-phenyl)-3-chloro-indol-1-ylmethyl]-phenoxy}-acetic acid ethyl ester

This procedure was performed analogously to that outlined for the synthesis of 3-methyl indole acetic acid ethyl esters outlined in method 3.
Mp = 90-94°C; ¹H NMR (DMSO) 7.45 (d , 4H, J= 7.8 Hz), 7.41 - 7.26 (m, 9H), 7.14 (d , 2 H , J = 8.7 Hz), 7.04 (d , 1 H , J = 2.4 Hz), 6.91 (dd, 1 H, J = 9.0Hz, J = 2.5 Hz), 6.80-6.74 (m, 4H), 5.24 (s , 2H), 5.15 (s , 2H), 5.14 (s , 2H), 4.66 (s , 2 H), 4.12 (q, 2H, J = 7.2 Hz), 1.16 (t , 3H , J = 7.5 Hz); MS el m/z 631(M+).

Example No. 145 Reduction of No. 144 to render No. 145 2-[4-[5-Benzylxy-2-(4-benzylxy-phenyl)-3-chloro-indol-1-ylmethyl]-phenoxy]-ethanol

This reaction was performed analogously to that outlined for the synthesis of 3-methyl indoles outlined in method 4. Compound was not purified or characterized, but used as obtained for the next step.

Example No. 146 Bromination of No. 145 to render Benzylxy-2-(4-benzylxy-phenyl)-1-[4-(2-bromo-ethoxy)-benzyl]-3-chloro-1H-indole

This reaction was performed analogously to that outlined for the synthesis of 3-methyl indoles outlined in method 5. Mp = 155-158°C; ¹H NMR (DMSO) 7.45 (d , 4 H, J= 7.8 Hz), 7.41 - 7.25 (m, 9H), 7.14 (d , 2 H , J = 8.7 Hz), 7.04 (d , 1 H , J = 2.4 Hz), 6.91 (dd, 1 H, J = 9.0Hz, J = 2.5 Hz), 6.74 (s, 4H), 5.24 (s , 2 H), 5.15 (s , 2H), 5.14 (s , 2 H), 4.20 (t,

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2 H, J = 5.3 Hz), 3.74 (t, 2 H, J = 5.3 Hz); MS el m/z 651 (M+).

Example No. 147 Substitution of No. 146 with piperidine to render 5-Benzylxy-2-(4-benzylxy-phenyl)-3-chloro-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole

This reaction performed analogously to that outlined for the synthesis of 3-methyl indoles outlined in method 6, using piperidine to substitute the bromide.
Mp 96-98°C; ¹H NMR (DMSO) 7.45 (d, 4 H, J = 7.8 Hz), 7.40 - 7.30 (m, 9 H), 7.14 (d, 2 H, J = 8.7 Hz), 7.04 (d, 1 H, J = 2.4 Hz), 6.91 (dd, 1 H, J = 9.0 Hz, J = 2.5 Hz), 6.74 (s, 4 H), 5.24 (s, 2 H), 5.15 (s, 2 H), 5.14 (s, 2 H), 3.93 (t, 2 H, J = 6.0 Hz), 2.56 (t, 2 H, J = 6.0 Hz), 2.41-2.32 (m, 4 H), 1.48-1.39 (m, 4 H), 1.38-1.31 (m, 2 H).

Example No. 148 5-Benzylxy-2-(4-benzylxy-phenyl)-3-chloro-1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-1H-indole

Reaction performed the same as above except the substituting amine used was hexamethyleneamine.
Mp = 94-97°C; ¹H NMR (DMSO) 7.45 (d, 4 H, J = 7.8 Hz), 7.42 - 7.30 (m, 9 H), 7.14 (d, 2 H, J = 8.7 Hz), 7.04 (d, 1 H, J = 2.4 Hz), 6.91 (dd, 1 H, J = 9.0 Hz, J = 2.5 Hz), 6.74 (s, 4 H), 5.24 (s, 2 H), 5.15 (s, 2 H), 5.14 (s, 2 H), 3.93 (t, 2 H, J = 6.0 Hz), 2.75 (t, 2 H, J = 6.0 Hz), 2.63-2.59 (m, 4 H), 1.58-1.44 (m, 8 H); MS el m/z 671 (M+).

Example No. 149 5-Benzylxy-2-(2-methyl-4-benzylxy-phenyl)-3-chloro-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole

Reactions to make this compound analogous to those used to make No. 147.
Oil; ¹H NMR(DMSO) 7.50 - 7.29 (m, 11 H), 7.17 (d, 1 H, J = 8.4 Hz), 7.05 (d, 1 H, J = 2.4 Hz), 7.02 (d, 1 H, J = 2.4 Hz), 6.93 - 6.85 (m, 2 H), 6.75 - 6.65 (m, 4 H), 5.14 (s, 2 H), 5.13 (s, 2 H), 5.07 (m, 2 H), 3.92 (t, 2 H, J = 5.9 Hz), 2.55 (t, 2 H, J = 5.9 Hz), 2.42 - 2.29 (m, 4 H), 1.94 (s, 3 H), 1.44 - 1.40 (m, 4 H), 1.38-1.34 (m, 2 H).

Example No. 133 3-Chloro-2-(4-hydroxy-phenyl)-1-[4-(2-pyrrolidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol (HCl)

Synthesized as described for example No. 134.
Mp = 233-235°C; ¹H NMR (DMSO) 10.50 (s, 1 H), 9.88 (s, 1 H), 9.01 (s, 1 H), 7.30-7.20 (m, 3 H), 6.90 - 6.80 (m, 7 H), 6.68 (dd, 1 H, J = 2.4, Hz, 8.8 Hz), 5.20 (s, 2 H), 4.22 (t, 2 H, J = 4.8 Hz), 3.47 (t, 2 H, J = 4.8 Hz), 3.10 (bm, 4 H), 1.90 (s, 4 H); IR (KBr) 3400, 1625, 1475, 825 cm⁻¹; MS el m/z 462 (M+); CHN calcd for C₂₇H₂₇ClN₂O₃ + 1 HCl + .75 H₂O.

Example No. 134 Removal of benzyl ethers to render 3-Chloro-2-(4-hydroxy-phenyl)-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol (HCl)

Benzyl ethers were removed analogously to that procedure outlined for 3-methyl indoles outlined in method 7. This compound was then converted to the hydrochloride salt as described previously in method 8; Mp = 207-209°C; ¹H NMR (DMSO) 10.10 (bs, 1 H), 9.86 (s, 1 H), 9.07 (s, 1 H), 7.26 (d, 2 H, J = 8.6 Hz), 7.22 (d, 1 H, J = 8.8 Hz), 6.87 (d, 2 H, J = 8.6Hz), 6.81 - 6.78 (m, 5 H), 6.65 (dd, 1 H, J = 8.8 Hz, J = 2.2 Hz), 5.20 (s, 2 H), 4.27 (t, 2H, J = 5.0Hz), 3.44 - 3.37 (m, 4 H), 3.00 -2.85 (m, 2 H), 1.81-1.60 (m, 5H), 1.41 - 1.26 (m, 1 H); IR (KBr) 3350, 1470, 1250 CM -1; MS el m/z 476 (M+); CHN calc for C₂₈H₂₉ClN₂O₃ + HCl + 1.5 H₂O.

Example No. 135 3-Chloro-2-(4-hydroxy-phenyl)-1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-1H-indol-5-ol (HCl)

Synthesized as described for No. 134.
Mp = 196-198°C; ¹H NMR (DMSO) 10.10 (brs, 1 H), 9.86 (s, 1 H), 9.07 (s, 1 H), 7.26 (d, 2 H, J = 8.8 Hz), 7.22 (d, 1 H, J = 9.0 Hz), 6.87 (d, 2 H, J = 8.6Hz), 6.84-6.78 (m, 5 H), 6.65 (dd, 1 H, J = 8.8 Hz, J = 2.2 Hz), 5.20 (s, 2 H), 4.27 (t, 2H, J = 5.0Hz), 3.45-3.30 (m, 4 H), 3.21-3.10 (m, 2 H), 1.82-1.76 (m, 4 H), 1.65 - 1.46 (m, 4 H); MS el m/z 491 (M+); CHN calc for C₂₉H₃₁ClN₂O₃ + 1 HCl + .37 H₂O; IR (KBr) 3400, 3200, 1450, 1125

Example No. 136 3-Chloro-2-(4-hydroxy-2-methyl-phenyl)-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol

Synthesized as described for No. 134 except the compound was not converted into a salt.
Foam; ¹H NMR (DMSO) 9.64 (s, 1 H), 9.01 (s, 1 H), 7.25 (d, 1 H, J = 8.8Hz), 7.03 (d, 1 H, J = 8.1 Hz), 6.79 (d, 1 H, J = 2.4 Hz), 6.78 - 6.65 (m, 7 H), 5.06 - 4.92 (m, 2 H), 3.94 (t, 2 H, J = 5.9 Hz), 2.62 - 2.57 (m, 2 H), 2.42 - 2.32 (m, 4 H), 1.90 (s, 3 H), 1.48- 1.40 (m, 4 H), 1.40 - 1.32 (m, 2 H); MS el m/z 490 (M+); IR (KBr) 3430, 2900, 1450 cm⁻¹; CHN calc for C₂₉H₃₁ClN₂O₃ + 1.0 H₂O.

Synthesis of 3-ethylindole analogue No. 137

This compound was synthesized in exact analogy to the example given for 3-methylindoles, supra, using methods a and 2-8. The only difference is that the starting material used is 4'-(benzyloxy)butyrophenone CAS No. [26945-71-1] instead of 4'-(benzyloxy)propiophenone. Data for intermediates is as follows.

Example No. 150 5-Benzyl-2-(4-benzyl-phenyl)-3-ethyl-1H-indole

Mp = 101 - 108°C; MS el m/z 433 (M+).

Example No. 151 {4-[5-Benzyl-2-(4-benzyl-phenyl)-3-ethyl-indol-1-ylmethyl]-phenoxy}-acetic acid ethyl ester

Mp = 72 - 75°C; MS el m/z 625 (M+).

Example No. 152 2-{4-[5-Benzyl-2-(4-benzyl-phenyl)-3-ethylindol-1-ylmethyl]-phenoxy}-ethanol

Mp = 105 - 113 °C; MS el m/z 583 (M+).

Example No. 153 Benzyl-2-(4-benzyl-phenyl)-1-[4-(2-bromoethoxy)-benzyl]-3-ethyl-1H-indole

Mp = 140°C (decomp.); MS el m/z 647, 645 (M+, Br present).

Example No. 154 5-Benzyl-2-(4-benzyl-phenyl)-3-ethyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole

Mp = 92 - 96°C; ^1H NMR (DMSO) 7.47 (d, 4 H, J = 7.2 Hz), 7.42 - 7.39 (m, 4 H), 7.36 - 7.30 (m, 2 H), 7.27 (d, 2 H, J = 8.6 Hz), 7.18 (d, 1 H, J = 8.8 Hz), 7.14 (d, 1 H, J = 2.4 Hz), 7.10 (d, 2 H, J = 8.8 Hz), 6.79 (dd, 1 H, J = 8.8 Hz, 2.2 Hz), 6.73 (s, 4 H), 5.13 (s, 2 H), 5.11 (s, 4 H), 3.93 (t, 2 H, J = 5.9 Hz), 2.62 - 2.53 (m, 4 H), 2.40 - 2.33 (m, 4 H), 1.49 - 1.42 (m, 4 H), 1.37 - 1.30 (m, 2 H), 1.10 (t, 3 H, J = 7.2 Hz); MS el m/z 650 (M+H+).

Example No. 137 2-(4-Hydroxy-phenyl)-3-ethyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol (HCl)

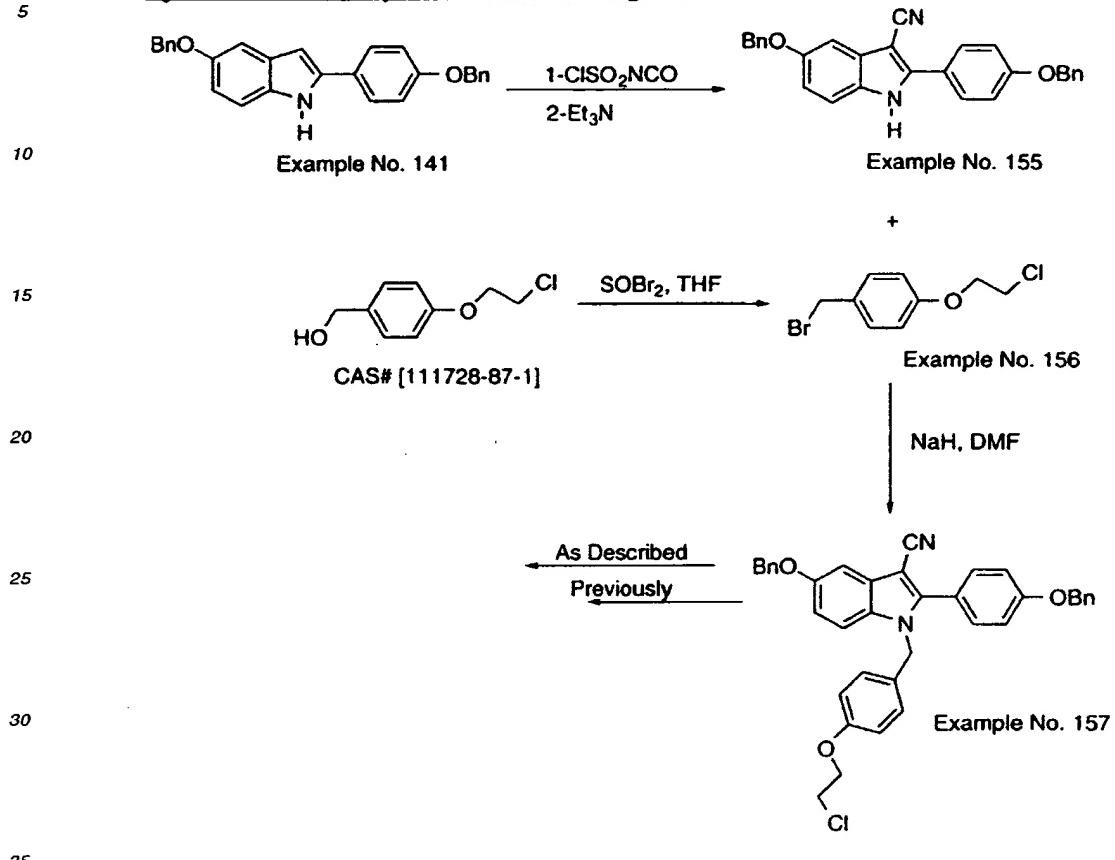
Mp = 160 - 164°C; ^1H NMR (DMSO) 9.78 (br s, 1 H), 9.69 (s, 1 H), 8.69 (s, 1 H), 7.14 (d, 2 H, J = 8.6 Hz), 7.05 (d, 1 H, J = 8.6 Hz), 6.87 - 6.78 (m, 7 H), 6.56 (dd, 1 H, J = 8.8 Hz, 2.4 Hz), 5.08 (s, 2 H), 4.25 (t, 2 H, J = 4.4 Hz), 3.45 - 3.38 (m, 5 H), 3.00 - 2.86 (m, 2 H), 2.57 - 2.50 (m, 2 H), 1.83 - 1.59 (m, 5 H), 1.41 - 1.28 (m, 1 H), 1.10 (t, 2 H, J = 7.5 Hz); IR (KBr) 3400 br, 3200 br, 2920, 1610 cm⁻¹; MS el m/z 470 (M+); CHN calcd for C₃₀H₃₄N₂O₃ + HCl + 1.5 H₂O.

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Scheme 15**Synthesis of 3-cyanoindole analogues****Example No. 155 5-Benzylxy-3-cyano-2-(4-benzylxy-phenyl)-1H-indole**

In a reaction flask 5-Benzylxy-2-(4-benzylxy-phenyl)-1H-indole No. 141 (5.90 g, 14.6 mmol) was mixed with CH_2Cl_2 (90 mL) was cooled down to 0°C (the starting material did not completely dissolve in CH_2Cl_2). While stirring vigorously, a solution of chlorosulfonyl isocyanate (2.26 g, 16.0 mmol) in CH_2Cl_2 (25 mL) was added dropwise over a period of 45 min. The reaction was run at 0°C for 2 hrs while detected by TLC for the formation of the insoluble N-chlorosulfonylamide intermediate. After this period, Et_3N (1.47 g, 14.6 mL) in CH_2Cl_2 (25 mL) was added dropwise over 45 min at 0°C. The insoluble residue became soluble in the reaction solvent as the Et_3N addition was approaching completion. The reaction was let go for the additional 1 hr at 0°C and 2 hrs at rt. The progress of the reaction could be observed by the insoluble solid formation of the product as the reaction time went on. The solvent was stripped down and the solid residue purified by trituration with methanol to yield (4.0 g, 63.8 %). Mp = 238 - 242°C; ^1H NMR (DMSO) 12.31 (s, 1 H), 7.88 (d, 2 H, J = 8.8 Hz), 7.48 (d, 4 H, J = 7.25 Hz), 7.55 - 7.30 (m, 7 H), 7.23 (d, 2 H, J = 8.8 Hz), 7.14 (d, 1 H, J = 2.4 Hz), 6.97 (dd, 1 H, J = 2.2 Hz, 8.8 Hz), 5.20 (s, 2 H), 5.17 (s, 2 H); MS el m/z 430 (M $^+$).

Example No. 156 4-(2-Chloroethoxy)benzylbromide

To 4-(2-Chloroethoxy)benzylalcohol CAS No. [111728-87-1] (6.4 g, 34.31 mmol) in dioxane (100 mL) at 0°C was added slowly thionylbromide (7.13 g, 34.31 mmol). The reaction was run at 0°C after 5 min. The reaction mixture was diluted with ether (200 mL) and washed with H_2O (1x30 mL) then NaHCO_3 (2x25 mL), and brine (30 mL). The organic extract was dried over MgSO_4 and concentrated. The crude product was purified by silica gel chromatography (15% EtOAc/Hex) to yield 5.0 g (58%) of the desired product. Mp = 64-66°C; ^1H NMR (DMSO) 7.37 (d, 2 H, J = 8.8 Hz),

6.93 (d, 2 H, J = 8.8 Hz), 4.68 (s, 2 H), 4.24 (t, 2 H, J = 5.05 Hz), 3.93 (t, 2 H, J = 5.27 Hz); MS el m/z 248 (M+).

Example No. 157 Benzylxy-2-(4-benzyloxy-phenyl)-1-[4-(2-chloroethoxy)-benzyl]-3-cyano-1H-indole

In a reaction flask the 3-cyano indole starting material No. 155 (2.86 g, 6.64 mmol) was dissolved in DMF (25 mL) at 0°C was added NaH (191.2 mg, 8 mmol) slowly. The reaction was stirred at 0°C for 20 min. In a separate reaction flask containing 4-(2-Chloroethoxy)benzylbromide No. 156 (1.81 g, 7.28 mmol) in DMF (15 mL) at 0°C, the above prepared indole anion solution taken up by syringe was added slowly. The reaction was stirred at 0 °C for 20 min and promoted to rt for 1 h. The reaction was quenched with a few drops of H₂O. The reaction mixture was partitioned between EtOAc (2x100 mL) and H₂O (80 mL). The organic extract was washed with brine (80 mL), dried over MgSO₄, and concentrated. The crude product was purified by trituration with ether to give the product as a white solid (2.80 g, 70.4%). Mp = 160-162°C; ¹H NMR (DMSO) 7.53 - 7.28 (m, 13 H), 7.23 (m, 3 H), 6.97 (dd, 1 H, J = 2.4 Hz, 9.0 Hz), 6.86 - 6.78 (m, 4 H), 5.37 (s, 2 H), 5.18 (s, 4 H), 4.15 (t, 2 H, J = 4.8 Hz), 3.87 (t, 2 H, J = 5.3 Hz); MS el m/z 598 (M+).

Example No.'s 158 and 159

Substitution of the chloro group with piperidine and hexamethyleneamine was performed analogously to the procedure outlined in method 6 using No. 157 as a starting material, *supra*.

Example No. 158 5-Benzylxy-2-(4-benzyloxy-phenyl)-3-cyano-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole

Mp = 148 - 150 °C; ¹H NMR (DMSO) 7.54 - 7.30 (m, 13 H), 7.25 - 7.18 (m, 3 H), 6.98 (dd, 1 H, J = 2.4 Hz, 9.0 Hz), 6.84 - 6.74 (m, 4 H), 5.35 (s, 2 H), 5.17 (s, 4 H), 3.94 (t, 2 H, 5.9 Hz), 2.55 (t, 2 H, 5.7 Hz), 2.35 (bs, 4 H), 1.50 - 1.40 (m, 4 H), 1.38 - 1.25 (m, 2 H); IR 3400, 2910, 2250, 1250 cm⁻¹; MS FAB 648 [M+H]⁺.

Example No. 159 5-Benzylxy-2-(4-benzyloxy-phenyl)-3-cyano-1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-1H-indole

¹H NMR (DMSO) 8.60 (br s, 1 H), 7.60 - 7.28 (m, 12 H), 7.25 - 7.16 (m, 3 H), 6.97 (dd, 1 H, J = 2.4 Hz, 9.0 Hz), 6.88 - 6.75 (m, 4 H), 5.35 (s, 2 H), 5.17 (s, 4 H), 3.92 (t, 2 H, J = 6.2 Hz), 3.08-3.00 (m, 2 H), 2.77 (t, 2 H, J = 5.9 Hz), 2.63 (t, 4 H, J = 4.8 Hz), 1.78 - 1.68 (m, 2 H), 1.60 - 1.40 (m, 4 H); MS el m/z 661 (M+).

Examples No. 138 and No. 139

Benzyl ethers were removed by hydrogen transfer using 1,4 cyclohexadiene and 10% Pd/C as described in method 7. Compounds were converted into their respective hydrochloride salts as described in method 8.

Example No. 138 5-Hydroxy-2-(4-Hydroxy-phenyl)-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole-3-carbonitrile (HCl)

Mp = 173 - 175°C; ¹H NMR (DMSO) 10.40 (s, 1 H), 10.12 (s, 1 H), 9.40 (s, 1 H), 7.38 (m, 2 H), 7.30 (d, 1 H, J = 8.8 Hz), 7.02 - 6.90 (m, 3 H), 6.88 (s, 4 H), 6.75 (dd, 1 H, J = 2.4 Hz, 9Hz), 5.33 (s, 2 H), 4.30 (t, 2 H, J = 4.8 Hz), 3.51 - 3.38 (m, 4 H), 2.92 (m, 2 H), 1.85 - 1.73 (m, 4 H), 1.68 - 1.59 (m, 1 H), 1.26 - 1.21 (m, 1 H); IR 3400, 2200, 1250 cm⁻¹; MS el m/z 467 (M+); CHN calcd for C₂₉H₂₉N₃O₃ + 1.0 HCl + 1.0 H₂O.

Example No. 139 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-5-hydroxy-2-(4-hydroxy-phenyl)-1H-indole-3-carbonitrile (HCl)

Mp = 160 - 163°C; ¹H NMR (DMSO) 10.22 (s, 1 H), 10.08 (s, 1 H), 9.35 (s, 1 H), 7.40 - 7.37 (m, 2 H), 7.30 (d, 1 H, 8.8 Hz), 7.0 - 6.90 (m, 3 H), 6.87 (s, 4 H), 6.74 (dd, 1 H, J = 2.41 Hz, 9 Hz), 5.33 (s, 2 H), 4.27 (t, 2 H, J = 5.0 Hz), 3.50 - 3.30 (m, 4 H), 3.20 (m, 2 H), 1.85 - 1.70 (m, 4 H), 1.65 - 1.50 (m, 4 H); IR 3300, 2200, 1250 cm⁻¹; MS el m/z 481 (M+); CHN calc for C₃₀H₃₁N₃O₃ + 1 HCl + 1 H₂O.

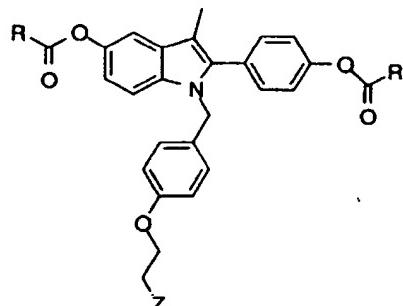
Esters of Indole No.'s 97 and 98

Table 9

20	No. 160	Et	
25	No. 161	t-Bu	
30	No. 162	t-Bu	

Method 9

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Example No. 162 Di-pivalate ester of 2-(4-Hydroxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol

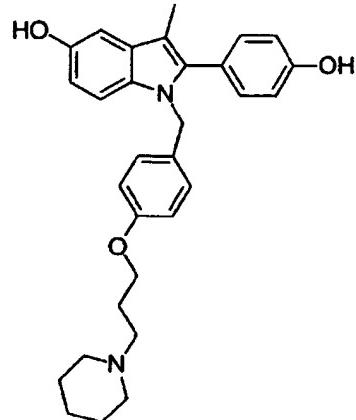
40 Example No. 97 free base was used as the starting material for this synthesis. No. 97 (1.0 g, 2.5 mmol) in 20 mL CH₂Cl₂ was treated with diisopropylethylamine (0.7g, 6.3 mmol) and catalytic DMAP. The reaction was cooled to 0°C and treated with pivaloyl chloride (0.7 mL, 5.6 mmol) and allowed to come to rt and stirred overnight. The reaction was worked up by diluting with CH₂Cl₂ and washing with water and brine. After drying over MgSO₄ the solution was concentrated and chromatographed on silica gel (MeOH/CH₂Cl₂, 1:19) to yield the desired material as an orange foam (1.08 g). This material was then taken up in 15 mL ethyl acetate and treated with 2.5 mL of a 1M HCl/Et₂O solution. Hexane was added until the solution turned cloudy. The product precipitated out as the HCl salt. This material was recrystallized from ethyl acetate/hexane to yield 0.42 g of pure No. 162: Mp = 182 - 185°C; CHN calcd for C₃₉H₄₈N₂O₅ + HCl + 0.25 H₂O.

Example No. 160 Di-propionate of 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-Indol-5-ol (HCl)

50 Compound was prepared analogously to example No. 162 except the starting material used was example No. 98 and the acylating agent used was propionyl chloride: Mp = 170.5 - 172°C; CHN calcd for C₃₆H₄₂N₂O₅ + HCl + 0.75 H₂O; MS FAB 605 (M+Na)+.

Example No. 161 Di-pivalate of 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol (HCl)

Compound was prepared analogously to example No. 162 except the starting material used was example No. 98:
 5 Mp = 143 - 151°C; CHN calcd for C₄₀H₅₀N₂O₅ + HCl + 0.75 H₂O.

Experimental for example No. 166

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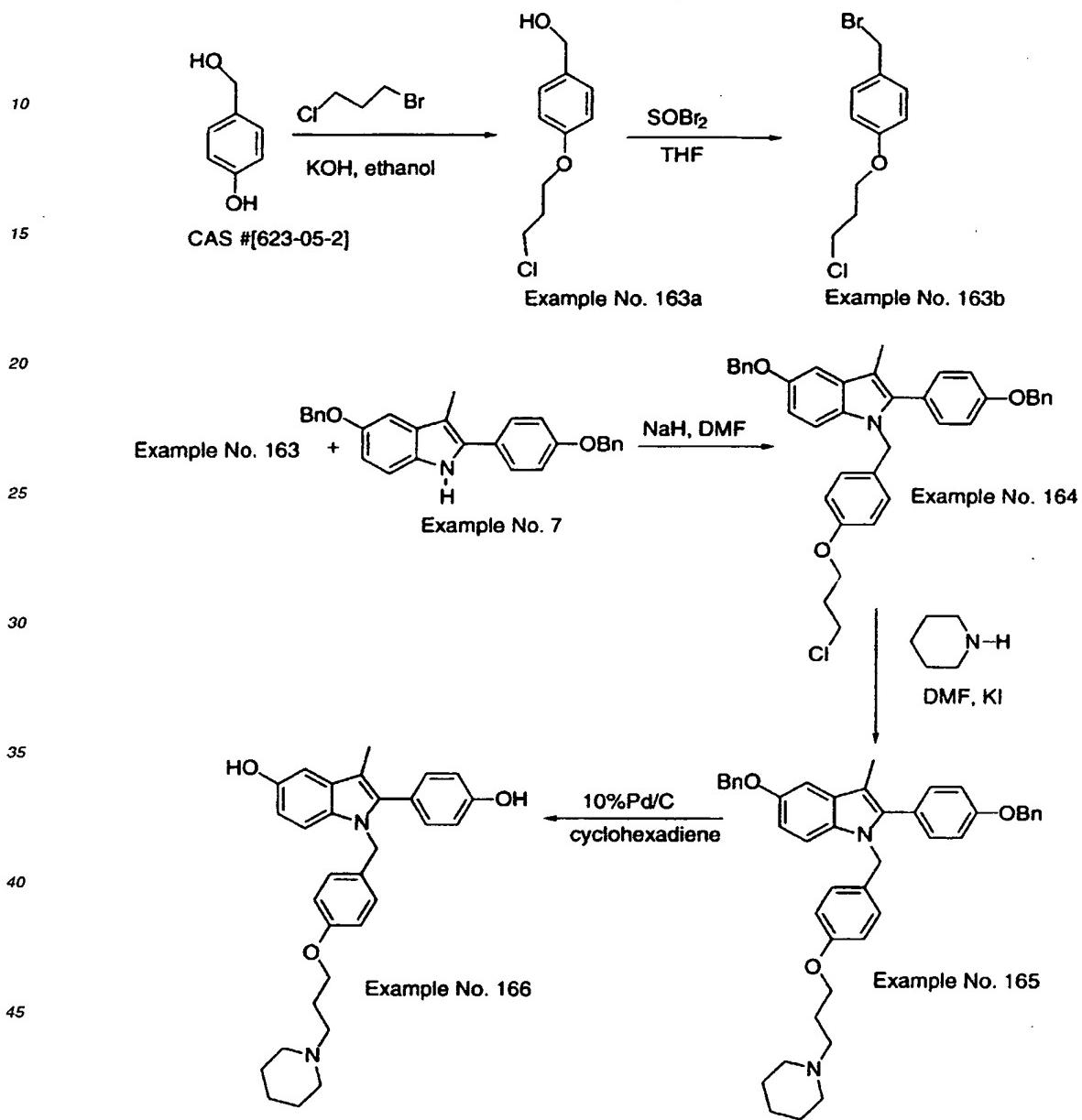
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Scheme 16
Synthesis of No. 166



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EXAMPLE No. 166

2-(4-Hydroxy-phenyl)-3-methyl-1-[4-[3-(piperidin-1-yl)-propoxy]-benzyl]-1H-indol-5-ol

The title compound was prepared according to Scheme 16 and the steps provided below:

Method 11**Example No. 163a 4-(3-chloropropoxy)-benzyl alcohol**

5 A solution of 4-hydroxy benzyl alcohol CAS No. [623-05-2] (10g, 80.5 mmol) in ethanol (70 mL) was treated with 1, 3 bromochloro propane (16.0g, 100 mmol) and potassium hydroxide (5.0 g, 89 mmol) was refluxed for 2 hours. The solution was cooled and filtered and then the filtrate concentrated. The concentrate was taken up in ether and washed with water, brine and dried over magnesium sulfate. The material was chromatographed on silica gel using ethyl acetate/hexanes (3:7) to yield 11.6 g of the product as a white solid: Mp = 65°C; ¹H NMR (DMSO) 7.21 (d, 2 H, J = 8.8 Hz),
10 6.88 (d, 2 H, J = 8.8 Hz), 5.03 (t, 1 H, J = 5.7 Hz), 4.40 (d, 2H, J = 5.5 Hz), 4.05 (t, 2H, J = 6. 1 Hz), 3.77 (t, 2 H, J = 6.4 Hz); MS el m/z 200.

Method 12**Example No. 163b 4-(3-chloropropoxy)-benzyl bromide**

15 A solution consisting of 4-(3-chloropropoxy)-benzyl alcohol No. 162 (10.6 g, 52.8 mmol) in dioxane (0.125 1) was cooled to 0° C and treated with a dropwise addition of thionyl bromide (12.0 g, 58.0 mmol). After 10 minutes the reaction was complete. The dioxane was diluted with ethyl ether and washed with water, brine, and then dried over MgSO₄.
20 The material was concentrated down to yield 15 g of an oil: ¹H NMR (DMSO) 7.36 (d, 2 H, J = 8.8 Hz), 6.92 (d, 2 H, J = 8.6 Hz), 4.68 (s, 2 H), 4.08 (t, 2 H, J = 5.9 Hz), 3.77 (t, 2 H, J = 6.4 Hz); MS (FAB) 266 (M+H⁺).

Method 13**Example No. 164 5-Benzylxy-2-(4-benzylxy-phenyl)-1-[4-(3-chloro-propoxy)-benzyl]-3-methyl-1H-indole**

25 A solution consisting of 5-Benzylxy-2-(4-benzylxy-phenyl)-3-methyl-1H-indole No. 7 (6.5 g, 15.5 mmol) in DMF (60 mL) was cooled to 0°C and treated with addition of sodium hydride (0.68 g, 17.0 mmol) and stirred for 20 minutes. A solution of 4-(3-chloropropoxy)-benzyl bromide No. 163 in DMF (10 mL) was then added slowly. The reaction was allowed to come to rt and stirred for 2 hours. The reaction was poured into water and extracted with ethyl acetate. The ethyl acetate was washed with water, brine and dried over magnesium sulfate and concentrated. The concentrate was treated with methanol and 5 g of the desired product precipitated as a white solid with a melting point of 130-132°C.

Method 14**Example No. 165 5-Benzylxy-2-(4-benzylxy-phenyl)-1-[4-(3-piperidin-1-yl-propoxy)-benzyl]-3-methyl-1H-Indole**

35 A solution of 5-Benzylxy-2-(4-benzylxy-phenyl)-1-[4-(3-chloro-propoxy)-benzyl]-3-methyl-1H-indole No. 164 (3g, 5.1 mmol), potassium iodide (2.5 g, 15.3 mmol) and piperidine (3.0 mL, 30.6 mmol) were heated in DMF (30 mL) at 40 100°C for 18 hours. The reaction was worked up by pouring into water and extracting with ethyl acetate. The organic layer was washed with water, brine and dried over magnesium sulfate. The solution was concentrated to an oil and the product precipitated out by adding methanol. The product was obtained as a white solid: Mp = 104-106°C; ¹H NMR (DMSO) 7.47 (d, 4 H, J = 7.5 Hz), 7.38 (q, 4 H, J = 7.9 Hz), 7.36-7.30 (m, 1 H), 7.28 (d, 2 H, J = 8.3 Hz), 7.19 (d, 1 H, J = 8.8 Hz), 7.12-7.10 (m, 4 H), 6.80 (dd, 1 H, J = 8.8, 2.0 Hz), 6.72 (s, 4 H), 5.14 (s, 2 H), 5.13 (s, 2 H), 5.11 (s, 2 H), 45 3.86 (t, 2 H, J = 6.4 Hz), 2.35-2.20 (m, 6 H), 2.14 (s, 3 H), 1.78-1.75 (m, 2 H), 1.47-1.42 (m, 4 H), 1.40-1.31 (m, 2 H); MS el m/z 650.

Method 15**Example No. 166 2-(4-Hydroxy-phenyl)-3-methyl-1-[4-[3-(piperidin-1-yl)-propoxy]-benzyl]-1H-indol-5-ol**

50 A solution of 5-Benzylxy-2-(4-benzylxy-phenyl)-1-[4-(3-piperidin-1-yl-propoxy)-benzyl]-3-methyl-1H-indole No. 165 (2.35 g) in tetrahydrofuran (25 mL) and ethanol (25 mL) was added to 2.3 g of 10% palladium on carbon. Cyclohexadiene (10 mL) was added and the reaction allowed to stir at room temperature for 18 hours. The catalyst was filtered through celite and the reaction mixture was concentrated and chromatographed on silica gel using dichloromethane/methanol (4:1) to elute the product (0.8 g) as a white foam: Mp = 125-130°C; ¹H NMR 9.68 (s, 1 H), 8.70 (s, 1 H), 7.15 (d, 2 H, J = 8.6 Hz), 7.05 (d, 1 H, J = 8.8 Hz), 6.85 (d, 2 H, J = 8.6 Hz), 6.80 (d, 1 H, J = 2.4 Hz), 45 6.74 (d,
55 6.68 (d, 1 H, J = 2.4 Hz), 3.86 (t, 2 H, J = 6.4 Hz), 2.35-2.20 (m, 6 H), 2.14 (s, 3 H), 1.78-1.75 (m, 2 H), 1.47-1.42 (m, 4 H), 1.40-1.31 (m, 2 H); MS el m/z 650.

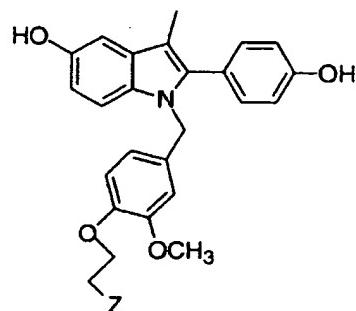
EP 0 802 183 A1

4 H, J = 2.6 Hz), 6.57 (dd, 1 H, J = 8.6, 2.2 Hz), 5.09 (s, 2 H), 3.88 (t, 2 H, J = 6.4 Hz), 3.60-3.15 (m, 2 H), 2.62-2.38 (m, 4 H), 2.09 (s, 3 H), 1.92-1.78 (m, 2 H), 1.55-1.43 (m, 4 H), 1.42-1.30 (m, 2 H); IR (KBr) 3400 (br), 2900, 1620, 1515 cm⁻¹; MS el m/z 470.

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Synthesis of No. 167 and No. 168

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Table 10

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No. 167	
No. 168	

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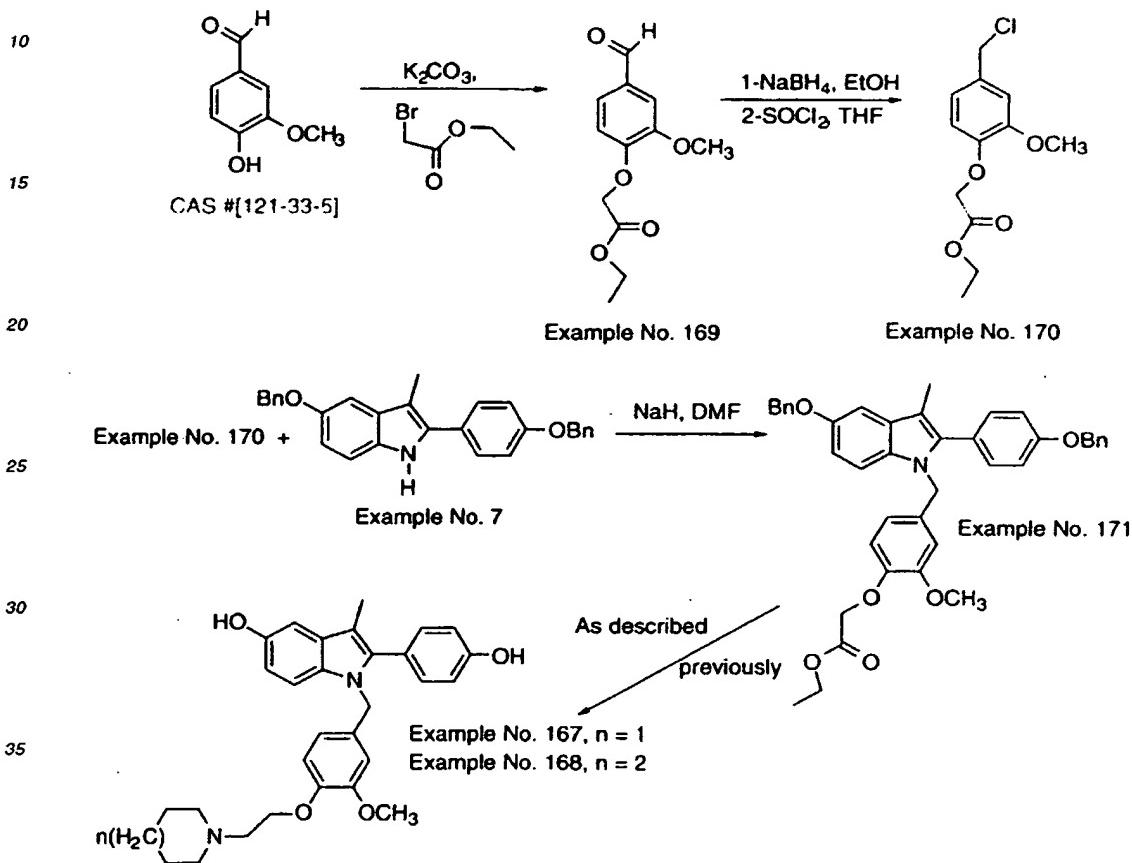
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Scheme 17

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Synthetic scheme for examples No. 167 and No. 168



Synthesis of example No. 167

2-(4-Hydroxy-phenyl)-1-[3-methoxy-4-(2-piperidin-1-yl-ethoxy)-benzyl]-3-methyl-1H-indol-5-ol

Example No. 169 (4-Formyl-2-methoxy-phenoxy)-acetic acid ethyl ester A flask containing vanillin (20g, 0.13 mol), ethyl bromoacetate (28.4g, 0.17 mol) and potassium carbonate (32.7 g, 0.24 mol) and acetone 200 mL were heated to reflux for 3 hours. The reaction was allowed to come to rt. The acetone was stripped off and the residue partitioned between water and ethyl acetate. The ethyl acetate was washed with brine and dried over magnesium sulfate. The organic layer was concentrated and the solid triturated with hexanes to yield 28.4 grams of example No. 169.

$\text{Mp} = 56 - 59^\circ\text{C}$; $^1\text{H NMR}$ (DMSO) 9.83 (s, 1 H), 7.50 (dd, 1 H, $J = 2.0$ Hz, 8.3 Hz), 7.42 (d, 1 H, $J = 1.7$ Hz), 7.07 (d, 1 H, $J = 8.4$ Hz), 4.91 (s, 2 H), 4.16 (q, 2 H, $J = 7.2$ Hz), 3.84 (s, 3 H), 1.20 (t, 3 H, $J = 7.1$ Hz); MS el m/z 298 (M^+); CHN calcd for $C_{12}H_{14}O_5$:

Example No. 170 (4-Chloromethyl-2-methoxy-phenoxy)-acetic acid ethyl ester

A solution of example No. 169 (28.8g, 0.119 mol) in 600 mL of EtOH/THF(1:1) was treated with sodium borohydride (2.25 g, 0.06 mol) at 0°C and stirred for 45 minutes. The solvents were evaporated and the reaction mixture diluted

with ethyl acetate and washed with 1N HCl solution. The product thus obtained (14.2 g, 0.059 mol) as an oil was dissolved in 140 mL of THF and cooled to 0°C. This solution was then treated with dropwise addition of thionyl chloride (7.38g, 0.062 mol) at 0°C. After 1 hour the reaction was poured into 400 mL of water and extracted with ether. The ether layer was washed with a sodium bicarbonate solution and dried over magnesium sulfate. This was concentrated and chromatographed by silica gel chromatography using ethyl acetate/hexanes (1:9). The product was obtained as 10.5 g of a white solid. Mp = 64-66°C; ¹H NMR (DMSO) 7.06 (d, 1 H, J = 2.0 Hz), 6.91 (dd, 1 H, J = 2.0 Hz, 2.2 Hz), 6.83 (d, 1 H, J = 2. Hz), 4.75 (s, 2 H), 4.70 (s, 2 H), 4.13 (q, 2 H, J = 7.2 Hz), 3.77 (s, 3 H), 1.19 (t, 3 H, J = 7.1 Hz); MS el m/z 258 (M+); CHN calcd for C₁₂H₁₅ClO₄.

10 **Example No. 171 {2-Methoxy-4-[5-benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-indol-1-yl[methyl]-phenoxy}-acetic acid ethyl ester**

Alkylation of the indole No. 7 was performed as described previously in Method No. 3 using example No. 170 as the electrophile.

15 Mp = 120 - 123°C; ¹H NMR (DMSO) 7.48 - 7.20 (m, 13 H), 7.18 - 7.10 (m, 3 H), 6.80 (dd, 1 H, J = 2.5 Hz, 8.8 Hz), 6.64 (d, 1 H, J = 8.4 Hz), 6.52 (d, 1 H, J = 2.0 Hz), 6.24 (dd, 1 H, J = 1.9 Hz, 8.1 Hz), 5.13 (s, 4 H), 5.10 (s, 2 H), 4.61 (s, 2 H), 4.10 (q, 2 H, J = 7.0 Hz), 3.58 (s, 3 H), 2.15 (s, 3 H), 1.15 (t, 3 H, J = 7.0 Hz); MS el m/z 641 (M+).

20 **Example No. 172 2-{2-Methoxy-4-[5-benzyloxy-2-(4-benzyloxyphenyl)-3-methyl-indol-1-yl[methyl]-phenoxy}-ethanol**

Reduction of the ester No. 171 was performed as described previously in Method 4. Mp = 86 - 90°C; ¹H NMR (DMSO) 7.48 - 7.20 (m, 13 H), 7.18 - 7.10 (m, 3 H), 6.80 (dd, 1 H, J = 2.5 Hz, 8.8 Hz), 6.64 (d, 1 H, J = 8.4 Hz), 6.52 (d, 1 H, J = 2.0 Hz), 6.24 (dd, 1 H, J = 1.9 Hz, 8.1 Hz), 5.13 (s, 4 H), 5.10 (s, 2 H), 4.76 (t, 1 H, J = 5.5 Hz), 3.83 (t, 2 H, J = 5.1 Hz), 3.63 (q, 2 H, J = 5.3 Hz), 3.56 (s, 3 H), 2.15 (s, 3 H); MS el m/z 599 (M+).

25 **Example No. 173 5-Benzyl-2-(4-benzyloxy-phenyl)-1-[3-methoxy-4-(2-bromo-ethoxy)-benzyl]-3-methyl-1H-Indole**

30 Conversion of the alcohol of example No. 172 to the bromide was performed analogously to that described in Method 5.

Mp = 150 - 152°C; ¹H NMR (DMSO) 7.48 - 7.20 (m, 13 H), 7.18 - 7.10 (m, 3 H), 6.80 (dd, 1 H, J = 2.5 Hz, 8.8 Hz), 6.64 (d, 1 H, J = 8.4 Hz), 6.52 (d, 1 H, J = 2.0 Hz), 6.24 (dd, 1 H, J = 1.9 Hz, 8.1 Hz), 5.13 (s, 4 H), 5.10 (s, 2 H), 4.15 (t, 2 H, J = 5.3 Hz), 3.70 (t, 2 H, J = 5.7 Hz), 3.58 (s, 3 H), 2.15 (s, 3 H); MS el m/z 661 (M+).

35 **Example No. 174 5-Benzyl-2-(4-benzyloxy-phenyl)-3-methyl-1-[3-Methoxy-4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-Indole**

Substitution of the bromide with piperidine was performed as described previously in Method 6.

40 ¹H NMR (DMSO) 7.48 - 7.20 (m, 13 H), 7.18 - 7.10 (m, 3 H), 6.80 (dd, 1 H, J = 2.5 Hz, 8.8 Hz), 6.64 (d, 1 H, J = 8.4 Hz), 6.52 (d, 1 H, J = 2.0 Hz), 6.24 (dd, 1 H, J = 1.9 Hz, 8.1 Hz), 5.13 (s, 4 H), 5.10 (s, 2 H), 3.90 (t, 2 H, J = 5.7 Hz), 3.55 (s, 3 H), 2.62 - 2.50 (bs, 2 H), 2.45 - 2.30 (bs, 4 H), 2.15 (s, 3 H), 1.50 - 1.40 (m, 4 H), 1.40 - 1.35 (m, 2 H); MS FAB m/z 667 (M+H+).

45 **Example No. 175 5-Benzyl-2-(4-benzyloxy-phenyl)-3-methyl-1-[2-Methoxy-4-(2-azepan-1-yl-ethoxy)-benzyl]-1H-Indole**

Reaction performed exactly as for No. 174 except hexamethyleneamine was used to displace the bromide in place of piperidine.

50 Foam; ¹H NMR (DMSO) 7.48 - 7.20 (m, 13 H), 7.18 - 7.10 (m, 3 H), 6.80 (dd, 1 H, J = 2.5 Hz, 8.8 Hz), 6.64 (d, 1 H, J = 8.4 Hz), 6.52 (d, 1 H, J = 2.0 Hz), 6.24 (dd, 1 H, J = 1.9 Hz, 8.1 Hz), 5.13 (s, 4 H), 5.10 (s, 2 H), 3.90 (t, 2 H, J = 5.7 Hz), 3.55 (s, 3 H), 2.85 - 2.70 (bs, 2 H), 2.70 - 2.55 (s, 4 H), 2.10 (s, 3 H), 1.60 - 1.15 (m, 8 H); MS FAB m/z 681 (M+H+)

55 **Example No. 167 2-(4-Hydroxy-phenyl)-1-[3-methoxy-4-(2-piperidin-1-yl-ethoxy)-benzyl]-3-methyl-1H-indol-5-ol**

Compound No. 173 was hydrogenated by transfer hydrogenation as described previously in Method 7. Compound was isolated as the hydrochloride salt by dissolving in ether and treating with 1.2 equivalents of 1N ether/HCl solution

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(this is a variation of method 8).

Mp = 123 - 127 °C; ^1H NMR (DMSO) 10.20 (bs, 1 H), 9.72 (s, 1 H), 8.71 (s, 1 H), 7.17 (d, 2 H, J = 8.6 Hz), 7.11 (d, 1 H, J = 8.8 Hz), 6.87 (d, 2 H, J = 8.6 Hz), 6.79 (m, 2 H), 6.57 (dd, 1 H, J = 2.4 Hz, 8.8 Hz), 6.55 (d, 1 H, J = 1.7 Hz), 6.33 (dd, 1 H, J = 1.7 Hz, 8.1 Hz), 5.11 (s, 2 H), 4.23 (t, 2 H, J = 4.8 Hz), 3.60 (s, 3 H), 3.45 (m, 2 H), 3.35 (m, 2 H), 2.95 (m, 2 H), 2.10 (s, 3 H), 1.70 (m, 5 H), 1.35 (m, 1 H); IR 3500, 1500, 1275 cm^{-1} ; MS (+) FAB m/z 487 (M+H)+; CHN calcd for $\text{C}_{30}\text{H}_{34}\text{N}_2\text{O}_4 + 1 \text{ HCl} + 1.0 \text{ H}_2\text{O}$.

Example No. 168 2-(4-Hydroxy-phenyl)-1-[3-methoxy-4-(2-azepan-1-yl-ethoxy)-benzyl]-3-methyl-1H-indol-5-ol

Prepared in the same way as that described for example No. 167.

Mp = 142 - 146 °C; ^1H NMR (DMSO) 10.36 (s, 1 H), 9.72 (s, 1 H), 8.71 (s, 1 H), 7.18 (d, 2 H, J = 8.3 Hz), 7.11 (d, 1 H, J = 8.6 Hz), 6.87 (d, 2 H, J = 8.3 Hz), 6.82 (d, 1 H, J = 8.1 Hz), 6.79 (d, 1 H, J = 2.2 Hz), 6.57 (dd, 1 H, J = 2.2 Hz, 8.6 Hz), 6.55 (d, 1 H, J = 1.8 Hz), 6.33 (dd, 1 H, J = 1.5 Hz, 8.1 Hz), 5.11 (s, 2 H), 4.24 (t, 2 H, J = 4.6 Hz), 3.60 (s, 3 H), 3.40 (m, 4 H), 3.20 (m, 2 H), 2.10 (s, 3 H), 1.75 (m, 4 H), 1.55 (m, 4 H); IR (KBr) 3300, 1500, 1270, 1200 cm^{-1} ; MS (+) FAB m/z 501 (M+H)+; CHN calcd for $\text{C}_{31}\text{H}_{36}\text{N}_2\text{O}_4 + 1.0 \text{ HCl} + 0.12 \text{ CH}_3\text{OH}$.

Biological Data

Method 16

In vitro estrogen receptor binding assay

Receptor preparation

CHO cells overexpressing the estrogen receptor were grown in 150 mm² dishes in DMEM + 10% dextran coated charcoal, stripped fetal bovine serum. The plates were washed twice with PBS and once with 10mM Tris-HCl, pH 7.4, 1mM EDTA. Cells were harvested by scraping the surface and then the cell suspension was placed on ice. Cells were disrupted with a hand-held motorized tissue grinder using two, 10-second bursts. The crude preparation was centrifuged at 12,000g for 20 minutes followed by a 60 minute spin at 100,000g to produce a ribosome free cytosol. The cytosol was then frozen and stored at -80°C. Protein concentration of the cytosol was estimated using the BCA assay with reference standard protein.

Binding assay conditions

The competition assay was performed in a 96-well plate (polystyrene*) which binds <2.0% of the total input [^3H]-17 β -estradiol and each data point was gathered in triplicate. 100uG/100uL of the receptor preparation was aliquoted per well. A saturating dose of 2.5 nM [^3H]17 β -estradiol + competitor (or buffer) in a 50 uL volume was added in the preliminary competition when 100x and 500x competitor were evaluated, only 0.8 nM [^3H] 17 β -estradiol was used. The plate was incubated at room temperature for 2.5 h. At the end of this incubation period 150 uL of ice-cold dextran coated charcoal (5% activated charcoal coated with 0.05% 69K dextran) was added to each well and the plate was immediately centrifuged at 99g for 5 minutes at 4°C. 200 uL of the supernatant solution was then removed for scintillation counting. Samples were counted to 2% or 10 minutes, whichever occurs first. Because polystyrene absorbs a small amount of [^3H]17 β -estradiol, wells containing radioactivity and cytosol, but not processed with charcoal were included to quantitate amounts of available isotope. Also, wells containing radioactivity but no cytosol were processed with charcoal to estimate unremovable DPM of [^3H] 17 β -estradiol. Coming No. 25880-96, 96-well plates were used because they have proven to bind the least amount of estradiol.

Analysis of results

Counts per minute (CPM) of radioactivity were automatically converted to disintegrated per minute (DPM) by the Beckman LS 7500 Scintillation Counter using a set of quenched standards to generate a H No. for each sample. To calculate the % of estradiol binding in the presence of 100 or fold 500 fold competitor the following formula was applied:

$$((\text{DPM sample}-\text{DPM not removed by charcoal}) / (\text{DPM estradiol}-\text{DPM not removed by charcoal})) \times 100\% = \% \text{ of estradiol binding}$$

For the generation of IC₅₀ curves, % binding is plotted vs compound. IC₅₀'s are generated for compounds that show >30% competition at 500x competitor concentration. For a description of these methods, see Hulme, E.C., ed. 1992. Receptor-Ligand Interactions: A Practical Approach. IRL Press, New York.(see especially chapter 8).

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Table 11**Estrogen Receptor Binding**

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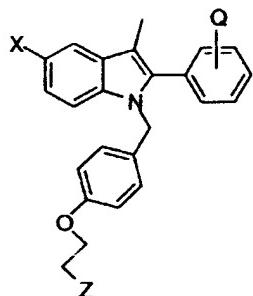
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No.	Substituent X	Substituent Z	IC ₅₀ (nM)
No. 85	H	H	0.45
No. 86	H	4'-OH	0.12
No. 87	OH	H	0.030
No. 88	OMe	4'-OH	0.35
No. 89	OH	4'-OMe	0.30
No. 90	OMe	4'-OMe	0.60
No. 91	OMe	4'-OMe	0.52
No. 92	OH	4'-OEt	0.062

Table 11 (Cont'd)

	No. 93	OH	4'-OEt		0.090
5	No. 94	F	4'-OH		0.20
10	No. 97	OH	4'-OH		0.060
15	No. 98	OH	4'-OH		0.050
20	No. 99	OH	4'-OH		0.03
25	No. 100	OH	4'-OH		0.06
30	No. 101	OH	4'-OH		0.04
35	No. 102	OH	4'-OH		0.08
40	No. 103	OH	4'-OH		0.2
45	No. 104	OH	4'-OH		0.1
50	No. 105	OH	4'-OH		0.028
55	No. 106	OH	4'-OH		0.1
	No. 107	OH	4'-OH		0.06

Table 11 (Cont'd)

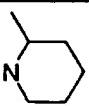
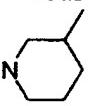
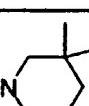
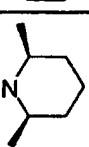
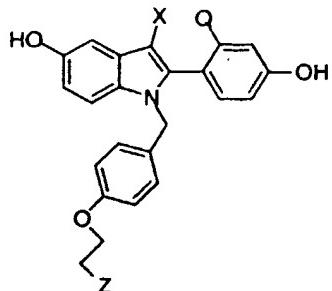
No.	Group	Structure	EC Number		
5	No. 108	OH	4'-OH		0.02
10	No. 109	OH	4'-OH		0.17
15	No. 110	OH	4'-OH		0.037
20	No. 111	OH	4'-OH		0.15
25	No. 112	OH	4'-OH		0.07
30	No. 113	OH	4'-OH		0.047
35	No. 114	OH	4'-OH		0.001
40	No. 115	OH	4'-OH		0.15
45	No. 116	OH	4'-Fl		0.04
50	No. 117	OH	4'-Fl		0.10
	No. 118	OH	3'-OMe,4'-OH		N/A
	No. 119	OH	3',4'-OCH ₂ O-		0.070

Table 11 (Cont'd)

5	No. 120	OH	4'-O-iPr	
10	No. 121	OH	4'-O-iPr	
15	No. 122	OH	4'-O-Cp	
20	No. 123	OH	4'-CF ₃	
25	No. 124	OH	4'-CH ₃	
30	No. 125	OH	4'-Cl	
35	No. 126	OH	2',4',-Dimethoxy	
40	No. 127	OH	3'-OH	
45	No. 128	OH	3'-OH	
50	No. 129	OH	4'-OH,3'-Fl	
55	No. 130	OH	4'-OH, 3'-Fl	
55	No. 131	OH	3'-OMe	
55	No. 132	OH	4'-OCF ₃	

Table 12

Estrogen Receptor Binding



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No. 133	Cl	H	N Cyclopentyl	0.004
No. 134	Cl	H	N Cyclohexyl	0.024
No. 135	Cl	H	N Cycloheptyl	0.029
No. 136	Cl	CH ₃	N Cyclohexyl	0.013
No. 137	Et	H	N Cyclohexyl	0.15
No. 138	CN	H	N Cyclohexyl	0.011
No. 139	CN	H	N Cyclohexyl	0.023

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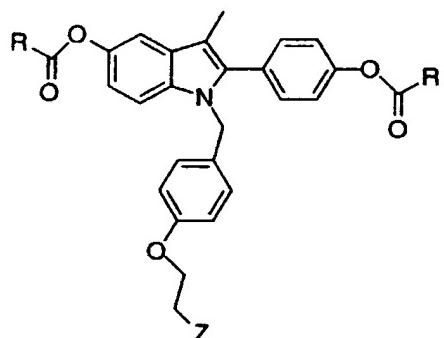
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Table 13**5 Estrogen Receptor Binding**

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Estrogen Receptor Binding Data			
Compound No.	Substituent R	Substituent Z	Binding Result
No. 160	Et	Ncyclohexyl	N/A
No. 161	t-Bu	Ncyclohexyl	N/A
No. 162	t-Bu	Ncyclohexyl	Does not Bind

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Table 14

Estrogen Receptor Binding

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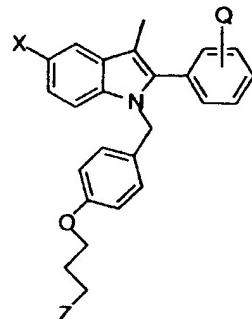
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No. 166	OH	4'-OH		0.099

Table 15

Estrogen Receptor Binding

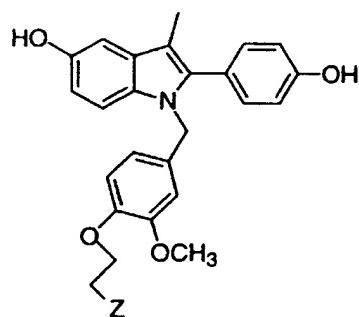
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No. 167		0.08
No. 168		0.057

Method 17**Ishikawa Cell Alkaline Phosphatase Assay****5 Cell Maintenance and Treatment:**

Ishikawa cells were maintained in DMEM/F12 (50%:50%) containing phenol red + 10% fetal bovine serum and the medium was supplemented with 2 mM Glutamax, 1% Pen/Strap and 1 mM sodium pyruvate. Five days prior to the beginning of each experiment (treatment of cells) the medium was changed to phenol red-free DMEM/F 12 + 10% dextran coated charcoal stripped serum. On the day before treatment, cells were harvested using 0.5% trypsin/EDTA and plated at a density of 5×10^4 cells/well in 96-well tissue culture plates. Test compounds were dosed at 10^{-6} , 10^{-7} and 10^{-8} M in addition to 10^{-6} M (compound) + 10^{-9} M 17β -estradiol to evaluate the ability of the compounds to function as antiestrogens. Cells were treated for 48 h prior to assay. Each 96-well plate contained a 17β -estradiol control. Sample population for at each dose was n=8.

15 Alkaline Phosphatase Assay:

At the end of 48h the media is aspirated and cells are washed three times with phosphate buffered saline (PBS). 50 μ L of lysis buffer (0.1 M Tris-HCl, pH 9.8, 0.2% Triton X-100) is added to each well. Plates are placed at -80°C for a minimum of 15 minutes. Plates are thawed at 37°C followed by the addition of 150 μ L of 0.1 M Tris-HCl, pH 9.8, containing 4 mM para-nitrophenylphosphate (pNPP) to each well (final concentration, 3 mM pNPP).

Absorbance and slope calculations were made using the KineticCalc Application program (Bio-Tek Instruments, Inc., Winooski, VT). Results are expressed as the mean +/- S.D. of the rate of enzyme reaction (slope) averaged over the linear portion of the kinetic reaction curve (optical density readings every 5 minutes for 30 minutes absorbance reading). Results for compounds are summarized as percent of response related to 1 nM 17β -estradiol.

Various compounds were assayed for estrogenic activity by the alkaline phosphatase method and corresponding ED50 values (95% C.I.) were calculated. The four listed in the following were used as reference standards:

30	17β -estradiol	0.03 nM
	17α -estradiol	1.42 nM
	estriol	0.13 nM
	estrone	0.36 nM

35 A description of these methods is described by Holinka, C.F., Hata, H., Kuramoto, H. and Gurge, E. (1986) Effects of steroid hormones and antiestrogens on alkaline phosphatase activity in human endometrial cancer cells (Ishikawa Line). Cancer Research, 46:2771-2774, and by Littlefield, B.A., Gurge, E., Markiewicz, L., McKinley, B. and Hochberg, R.B. (1990) A simple and sensitive microtiter plate estrogen bioassay based on stimulation alkaline phosphatase in Ishikawa cells; Estrogen action of D5 adrenal steroids. Endocrinology, 6:2757-2762.

40 Ishikawa Alkaline Phosphatase Assay

45	Compound	% Activation
	17β -estradiol	100% activity
	tamoxifen	0% activity (45% with 1 nM 17β -estradiol)
	raloxifene	5% activity (5% with 1 nM 17β -estradiol)
	Example No. 98	1% activity (1% with 1 nM 17β -estradiol)

50 Method No. 18**2X VIT ERE Infection Assay****55 Cell Maintenance and Treatment**

Chinese Hamster Ovary cells (CHO) which had been stably transfected with the human estrogen receptor were maintained in DMEM + 10% fetal bovine serum (FBS). 48h prior to treatment the growth medium was replaced with

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DMEM lacking phenol red + 10% dextran coated charcoal stripped FBS (treatment medium). Cells were plated at a density of 5000 cells/well in 96-well plates containing 200 μ L of medium/well.

Calcium Phoshate Transfection

5 Reporter DNA (Promega plasmid pGL2 containing two tandem copies of the vitellogenin ERE in front of the minimal thymidine kinase promoter driving the luciferase gene) was combined with the B-galactosidase expression plasmid pCH110 (Pharmacia) and carrier DNA (pTZ18U) in the following ratio:

10 10uG of reporter DNA
5uG of pCH110DNA
5 uG of pTZ18U
20 uG of DNA/1 mL of transfection solution

15 The DNA (20uG) was dissolved in 500 μ L of 250 mM sterile CaCl_2 and added dropwise to 500 μ L of 2 X HeBS (0.28 M NaCl, 50 mM HEPES, 1.5 mM Na_2HPO_4 , pH 7.05) and incubated at room temperature for 20 minutes. 20 μ L of this mixture was added to each well of cells and remained on the cells for 16 h. At the end of this incubation the precipitate was removed, the cells were washed with media, fresh treatment media was replaced and the cells were treated with either vehicle, 1 nM 17 β -estradiol, 1uM compound or 1 uM compound + 1 nM 17 β -estradiol (tests for estrogen antagonism). Each treatment condition was performed on 8 wells (n=8) which were incubated for 24 h prior to the luciferase assay.

Luciferase Assay

25 After 24h exposure to compounds, the media was removed and each well washed with 2 X with 125 μ L of PBS lacking Mg^{++} and Ca^{++} . After removing the PBS, 25 μ L of Promega lysis buffer was added to each well and allowed to stand at room temperature for 15 min, followed by 15 min at -80°C and 15 min at 37°C. 20 μ L of lysate was transferred to an opaque 96 well plate for luciferase activity evaluation and the remaining lysate (5 μ L) was used for the B-galactosidase activity evaluation (normalize transfection). The luciferan substrate (Promega) was added in 100 μ L aliquots to each well automatically by the luminometer and the light produced (relative light units) was read 10 seconds after addition.

Infection Luciferase Assay (Standards)

Compound	% Activation
17 β -estradiol	100% activity
estriol	38% activity
tamoxifen	0% activity (10% with 1 nM 17 β -estradiol)
raloxifene	0% activity (0% with 1 nM 17 β -estradiol)

B-Galactosidase Assay

45 To the remaining 5 μ L of lysate 45 μ L of PBS was added. Then 50 μ L of Promega B-galactosidase 2X assay buffer was added, mixed well and incubated at 37°C for 1 hour. A plate containing a standard curve (0.1 to 1.5 milliunits in triplicate) was set up for each experimental run. The plates were analyzed on a Molecular Devices spectrophotometric plate reader at 410 nm. The optical densities for the unknown were converted to milliunits of activity by mathematical extrapolation from the standard curve.

50 **Analysis of Results**

55 The luciferase data was generated as relative light units (RLUs) accumulated during a 10 second measurement and automatically transferred to a JMP (SAS Inc) file where background RLUs were subtracted. The B-galactosidase values were automatically imported into the file and these values were divided into the RLUs to normalize the data. The mean and standard deviations were determined from a n=8 for each treatment. Compounds activity was compared to 17 β -estradiol for each plate. Percentage of activity as compared to 17 β -estradiol was calculated using the formula

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%=((Estradiol-control)/(compound value)) X 100. These techniques are described by Tzukerman, M.T., Esty, A., Santiso-Mere, D., Danielian, P., Parker, M.G., Stein, R.B., Pike, J.W. and McDonnel, D.P. (1994). Human estrogen receptor transactivational capacity was determined by both cellular and promoter context and mediated by two functionally distinct intramolecular regions (see Molecular Endocrinology, 8:21-30).

5

Table 16
Infection Luciferase Activity

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No.	Control	Compound
No. 85	-2	43
No. 86	-5	2
No. 87	0	0
No. 88	4	44
No. 89	16	18
No. 90	3	58
No. 91	-3	56
No. 92	-4	-2
No. 93	-3	-2
No. 94	-5	15
No. 95	-4	-4
No. 96	12	8
No. 97	-4	-5
No. 98	5	5
No. 99	5	6
No. 100	9	10
No. 101	14	9
No. 102	9	10
No. 103	13	10
No. 104	7	7
No. 105	5	5
No. 106	10	81
No. 107	-1	54

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No. 108	11	10
No. 109	6	5
No. 110	8	10
No. 111	25	23
No. 112	10	10
No. 113	14	16
No. 114	1	-1
No. 115	11	10
No. 116	-1	1
No. 117	0	1
No. 118	N/A	N/A
No. 119	-1	-1
No. 120	-1	1
No. 121	0	1
No. 122	1	5
No. 123	-1	1

Table 16 (Cont'd)
Infection Luciferase Activity

		(100 uG compound + 1 uG 17 β -estradiol)
No. 124	-2	-2
No. 125	-3	-2
No. 126	-1	0
No. 127	-3	-4
No. 132	-5	-2
No. 133	7	9
No. 134	9	5
No. 135	7	3
No. 136	16	10
No. 137	6	8
No. 138	-2	-1
No. 139	-12	-13
No. 160	N/A	N/A
No. 161	N/A	N/A
No. 162	-14	-13
No. 166	25	23
No. 167	4	10
No. 168	3	7

Method No. 19

Rat Uterotrophic/Antiuterotrophic Bioassay

The estrogenic and antiestrogenic properties of the compounds were determined in an immature rat uterotrophic assay (4 day) that (as described previously by L.J.Black and R.L.Goode, Life Sciences, **26**, 1453 (1980)). Immature Sprague-Dawley rats (female, 18 days old) were tested in groups of six. The animals were treated by daily ip injection with 10 uG compound, 100 uG compound, (100 uG compound + 1 uG 17 β -estradiol) to check antiestrogenicity, and 1 uG 17 β -estradiol, with 50% DMSO/50% saline as the injection vehicle. On day 4 the animals were sacrificed by CO₂ asphyxiation and their uteri were removed and stripped of excess lipid, any fluid removed and the wet weight determined. A small section of one horn was submitted for histology and the remainder used to isolate total RNA in order

to evaluate complement component 3 gene expression.

Table 17

3 Day Rat Immature Uterine Assay

	<u>Uterine wt</u> mg	<u>Uterine wt</u> mg	<u>Uterine wt</u> mg	<u>Uterine wt</u> mg
--	-------------------------	-------------------------	-------------------------	-------------------------

Tamoxifen	71.4 mg	N/A	98.2 mg	42.7 mg
No. 85	41.1 mg	92.4 mg	94.4 mg	26.6 mg
No. 94	28.1 mg	93.7 mg	88.5 mg	22.3 mg
No. 97	27.4 mg	24.3 mg	63.2 mg	30.7 mg
No. 98	29.4 mg	27.9 mg	94.1 mg	35.9 mg
No. 100	59.9 mg	68.7 mg	91.9 mg	23.4 mg
No. 101	65.1 mg	71.0 mg	113.7 mg	27.7 mg
No. 122	46.7 mg	38.7 mg	103.4 mg	30.3 mg
No. 123	39.2 mg	61.4 mg	94.4 mg	26.1 mg
No. 138	28.4 mg	37.9 mg	93.9 mg	24.6 mg
No. 139	30.4 mg	45.0 mg	82.1 mg	20.5 mg
No. 168	43.2 mg	81.7 mg	98.9 mg	25.5 mg

Method No. 20

6-Week Ovariectomized Rat Model

Female Sprague Dawley CD rats, ovx or sham ovx, were obtained 1 day after surgery from Taconic Farm (weight range 240 - 275 g). They were housed 3 or 4 rats/cage in a room on a 14/10 (light/dark) schedule and provided with food (Purina 500 rat chow) and water ad libitum. Treatment for all studies began 1 day after the animals arrival and dosed 5 or 7 days per week as indicated for 6 weeks. A group of age matched sham operated rats not receiving any treatment served as an intact, estrogen replete control group for each study. All treatments were prepared in 1% tween 80 in normal saline at defined concentrations so that the treatment volume was 0.1mL/100g body weight. 17-beta estradiol was dissolved in corn oil (20 uG/mL) and delivered subcutaneously, 0. 1 mL/rat. All dosages were adjusted at three week intervals according to group mean body weight measurements.

Five weeks after the initiation of treatment and one week prior to the termination of the study, each rat was evaluated for bone mineral density (BMD). The BMD's of the proximal tibiae (PT) and fourth lumbar vertabrate (L4) were measured in anesthetized rats using a dual energy X-ray absorptiometer (Eclipse XR-26, Norland Corp. Ft. Atkins, WI). The dual energy X-ray absorptiometer (DXA) measurements for each rat were performed as follows: Fifteen minutes prior to DXA measurements, the rat was anesthetized with an intraperitoneal injection of 100 mg/kg ketamine (Bristol Laboratories, Syracuse, NY) and 0.75 mg/kg acepromazine (Aveco, Ft.Dodge, IA). The rat was placed on an acrylic table under the DXA scanner perpendicular to its path; the limbs were extended and secured with paper tape to the surface of the table. A preliminary scan was performed at a scan speed of 50 mm/second with a scan resolution of 1.5 mm X 1.5 mm to determine the region of interest in PT and L4. Small subject software was employed at a scan speed of 10mm/second with resolution of 0.5 mm X 0.5 mm for final BMD measurements. The software allows the operator to define a 1.5 cm wide area to cover the total length of L4. The BMDs for respective sites were computed by the software as a function of the attenuation of the dual beam (46.8 KeV and 80 KeV) X-ray generated by the source underneath the subject and the detector travelling along the defined area above the subject. The data for BMD values (expressed in g/cm²) and individual scans were stored for statistical analysis.

One week after BMD evaluation the rats were sacrificed by carbon dioxide suffocation and blood collected for cholesterol determination. The uteri were removed and the weights taken. Total cholesterol is determined using a Boehringer-

Mannheim Hitachi 911 clinical analyzer using the Cholesterol/HP kit. Statistics were compared using one-way analysis of variance with Dunnet's test.

Table 18

6-Week Ovariectomized Rat Study Of Example No. 98					
	Treatment		Δ Body Weight (g) ^{a,c}	Uterine Weight (mg) ^{a,c}	Cholesterol (mg/ dl) ^{a,c}
	Proximal Tibia	L ₄			
Study ^d					
Sham (Intact)	0.211** ± 0.003	0.183* ± 0.003	43.0* ± 6.0	426.4** ± 25.0	71.6** ± 5.0
Vehicle (Ovx)	0.189 ± 0.004	0.169 ± 0.004	62.7 ± 8.2	118.2 ± 7.8	87.2 ± 3.0
Example No. 98					
0.3mg/kg, p.o.	0.210** ± 0.003	0.1x73 ± 0.003	46.8 ± 6.6	149.3 ± 4.4	59.0** ± 2.2
Raloxifene 3mg/ kg, p.o.	0.207** ± 0.006	0.170 ± 0.003	25.3** ± 5.4	191.6** ± 9.3	55.0** ± 2.4
17 β -Estradiol 2 μ g/rat, s.c.	0.224** ± 0.004	0.169 ± 0.004	33.1** ± 4.9	426.0** ± 18.4	95.5 ± 3.9

^a Mean \pm SEM

^b Following 5 weeks of treatment

^c Following 6 weeks of treatment

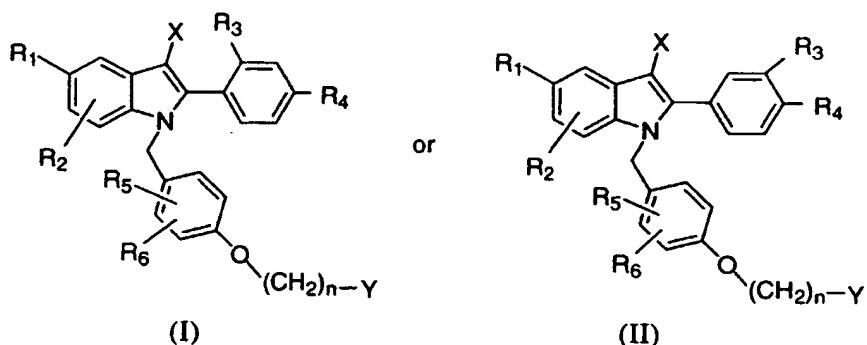
^d Daily treatment x7 days/week x6 weeks

* p < 0.05 vs corresponding Vehicle value

** p < 0.01 vs corresponding Vehicle value

Claims

1. A compound of formula I or II:



wherein:

R₁ is selected from H, OH or a C₁-C₁₂ ester (straight chain or branched) or C₁-C₁₂ (straight chain or branched or cyclic) alkyl ether thereof, or halogen: or a C₁-C₄ halogenated ether including trifluoromethyl ether and trichloromethyl ether.

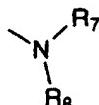
R₂, R₃, R₄, R₅, and R₆ are independently selected from H, OH or the C₁-C₁₂ esters (straight chain or branched) or C₁-C₁₂ alkyl ethers (straight chain or branched or cyclic) thereof, halogens, or C₁-C₄ halogenated ethers including trifluoromethyl ether and trichloromethyl ether, cyano, C₁-C₆ alkyl (straight chain or branched), or trifluoromethyl, with the proviso that, when R₁ is H, R₂ is not OH.

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X is selected from H, C₁-C₆ alkyl, cyano, nitro, trifluoromethyl, halogen;
 n is 2 or 3;
 Y is selected from:

- 5 a) the moiety:

10



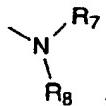
wherein R₇ and R₈ are independently selected from the group of H, C₁-C₆ alkyl, or phenyl optionally substituted by CN, C₁-C₆ alkyl (straight chain or branched), C₁-C₆ alkoxy (straight chain or branched), halogen, -OH, -CF₃, or -OCF₃; R₇ and R₈ are concatenated together as -(CH₂)_p-, wherein p is an integer of from 2 to 6, preferably 4 to 6, the ring so formed is optionally substituted with 1-3 substituents selected from a group containing C₁-C₃ alkyl, trifluoromethyl, halogen, hydrogen, phenyl, nitro, -CN
 b) a five, six or seven -membered saturated, unsaturated or partially unsaturated heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NH-, -N(C₁-C₄ alkyl)-, -N=, and -S(O)_m-, wherein m is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ acyloxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, -CO₂H-, -CN, -CONHR₁, -NH₂, C₁-C₄ alkylamino, di-(C₁-C₄alkyl)amino, -NHSO₂R₁, -NHCOR₁, -NO₂ and phenyl optionally substituted with 1-3 (C₁-C₄)alkyl;
 c) a bicyclic heterocycle containing from 6-12 carbon atoms either bridged or fused and containing up to two heteroatoms selected from the group consisting of -O-, -NH-, -N(C₁C₄ alkyl)-, and -S(O)_m-, wherein m is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ acyloxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, -CO₂H-, -CN-, -CONHR₁, -NH₂, C₁-C₄ alkylamino, di-(C₁-C₄alkyl)amino, -NHSO₂R₁, -NHCOR₁, -NO₂, and phenyl optionally substituted with 1-3 (C₁-C₄) alkyl;

and the pharmaceutically acceptable salts thereof.

- 35 2. A compound of Claim 1 wherein:

R₁ is selected from H, OH or the C₁-C₄ esters or alkyl ethers thereof or halogen;
 R₂, R₃, R₄, R₅, and R₆ are independently selected from H, OH or the C₁-C₄ esters or alkyl ethers thereof, halogen, cyano, C₁-C₆ alkyl, or trifluoromethyl, with the proviso that, when R₁ is H, R₂ is not OH;
 40 X is selected from H, C₁-C₆ alkyl, cyano, nitro, trifluoromethyl or halogen;
 Y is the moiety

45



50 R₇ and R₈ are selected independently from H, C₁-C₆ alkyl, or combined by -(CH₂)_p-, wherein p is an integer of from 2 to 6, so as to form a ring, the ring being optionally substituted by up to three substituents selected from the group of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, -CO₂H, -CN, -CONH(C₁-C₄), -NH₂, C₁-C₄ alkylamino, di(C₁-C₄)alkylamino, -NHSO₂(C₁-C₄), -NHCO(C₁-C₄), and -NO₂;

55 or a pharmaceutically acceptable salt thereof.

3. A compound of Claim 1 wherein:

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R₁ is OH;

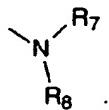
R₂, R₃, R₄, R₅, and R₆ are independently selected from H, OH or the C₁-C₄ esters or alkyl ethers thereof, halogen, cyano, C₁-C₆ alkyl, or trifluoromethyl, with the proviso that, when R₁ is H, R₂ is not OH;

X is selected from the group of Cl, NO₂, CN, CF₃, or CH₃;

Y is the moiety

5

10



and

15 R₇ and R₈ are concatenated together as -(CH₂)_r-, wherein r is an integer of from 4 to 6, to form a ring optionally substituted by up to three substituents selected from the group of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, -CO₂H, -CN, -CONH(C₁-C₄), -NH₂, C₁-C₄ alkylamino, di(C₁-C₄)alkylamino, -NHSO₂(C₁-C₄), -NHCO(C₁-C₄), and -NO₂;

20

or a pharmaceutically acceptable salt thereof.

4. A compound of Claim 1 which is one of the following:

25 5-Benzyl-2-(4-benzyloxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole or a pharmaceutically acceptable salt thereof;

30 5-Benzyl-2-(4-benzyloxy-phenyl)-3-methyl-1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-1H-indole or a pharmaceutically acceptable salt thereof;

35 5-Benzyl-2-(4-benzyloxy-phenyl)-3-methyl-1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-1H-indole or a pharmaceutically acceptable salt thereof;

40 5-Benzyl-2-(4-benzyloxy-phenyl)-3-methyl-1-[4-(2-diisopropylamino-1-yl-ethoxy)-benzyl]-1H-indole or a pharmaceutically acceptable salt thereof;

45 5-Benzyl-2-(4-benzyloxy-phenyl)-3-methyl-1-[4-(2-butyl-methylamino-1-yethoxy)-benzyl]-1H-indole or a pharmaceutically acceptable salt thereof;

50 5-Benzyl-2-(4-benzyloxy-phenyl)-3-methyl-1-[4-(4-dimethylamino)-ethoxy]-benzyl]-1H-indole or a pharmaceutically acceptable salt thereof;

55 5-Benzyl-2-(4-benzyloxy-phenyl)-3-methyl-1-[4-[2-(2-methyl-piperidin-1-yl)-ethoxy]-benzyl]-1H-indole or a pharmaceutically acceptable salt thereof;

5-Benzyl-2-(4-benzyloxyphenyl)-3-methyl-1-[4-[2-(3-methyl-piperidin-1-yl)-ethoxy]-benzyl]-1H-indole or a pharmaceutically acceptable salt thereof;

5-Benzyl-2-(4-benzyloxyphenyl)-3-methyl-1-[4-[2-(4-methyl-piperidin-1-yl)-ethoxy]-benzyl]-1H-indole or a pharmaceutically acceptable salt thereof;

5-Benzyl-2-(4-benzyloxyphenyl)-3-methyl-1-[4-[2-((cis)-2,6-Dimethyl-piperidin-1-yl)-ethoxy]-benzyl]-1H-indole or a pharmaceutically acceptable salt thereof;

5-Benzyl-2-(4-benzyloxyphenyl)-3-methyl-1-[4-[2-(1,3,3-trimethyl-6-azabicyclo[3.2.1]oct-6-yl)-ethoxy]-benzyl]-1H-indole or a pharmaceutically acceptable salt thereof;

(1S,4R)-5-Benzyl-2-(4-benzyloxyphenyl)-3-methyl [4-[2-(2-Aza-hicyclo[2.2.1]hept-2-yl)-ethoxy]-benzyl]-

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1H-indole or a pharmaceutically acceptable salt thereof;

5-Benzyl-2-(4-fluorophenyl)-3-methyl-1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-1H-indole or a pharmaceutically acceptable salt thereof;

5-Benzyl-2-(4-fluorophenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole or a pharmaceutically acceptable salt thereof;

5-Benzyl-2-(4-chlorophenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole or a pharmaceutically acceptable salt thereof;

5-Benzyl-2-[3,4-methylenedioxy-phenyl]-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole or a pharmaceutically acceptable salt thereof;

5-Benzyl-2-[4-isopropoxy-phenyl]-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole or a pharmaceutically acceptable salt thereof;

5-Benzyl-2-[4-methylphenyl]-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole or a pharmaceutically acceptable salt thereof;

1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-5-benzyl-2-(3-benzyl-phenyl)-3-methyl-1H-indole or a pharmaceutically acceptable salt thereof;

5-Benzyl-2-(4-benzyl-3-fluoro-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole or a pharmaceutically acceptable salt thereof;

5-Benzyl-2-(4-benzyl-3-fluoro-phenyl)-3-methyl-1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-1H-indole or a pharmaceutically acceptable salt thereof;

5-Benzyl-2-(3-methoxyphenyl)-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-3-methyl-1H-indole or a pharmaceutically acceptable salt thereof;

5-Benzyl-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-2-(4-trifluoromethoxyphenyl)-1H-indole or a pharmaceutically acceptable salt thereof;

(2-{4-[5-Benzyl-2-(4-benzyl-phenyl)-3-methyl-indol-1-ylmethyl]-phenoxy}-ethyl)-cyclohexyl-amine or a pharmaceutically acceptable salt thereof,

5-Benzyl-2-(4-benzyl-phenyl)-3-methyl-1-[4-methylpiperazin-1-yl]-ethoxy]-benzyl]-1H-indole or a pharmaceutically acceptable salt thereof;

1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-5-benzyl-2-(3-methoxy-phenyl)-3-methyl-1H-indole or a pharmaceutically acceptable salt thereof;

4-[3-Methyl-1-[4-(2-piperidin-1-yl-ethoxy)benzyl]-1H-indole] (HCl);

4-[3-Methyl-1-[4-(2-piperidin-1-yl-ethoxy)benzyl]-1H-indol-2-yl]-phenol hydrochloride (HCl);

3-Methyl-2-phenyl-1-[4-(2-piperidine-1-yl-ethoxy)benzyl]-1H-indol-5-ol (HCl);

4-[5-Methoxy-3-methyl-1-[4-(2-piperidin-1-yl)ethoxy]benzyl]-1H-indol-2-yl]phenol or a pharmaceutically acceptable salt thereof;

2-(4-methoxyphenyl)-3-methyl-1-[4-(2-piperidin-1-yl)-ethoxy]benzyl]-1H-indol-5-ol or a pharmaceutically acceptable salt thereof;

5-Methoxy-2-(4-methoxyphenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)benzyl]-1H-indole (HCl);

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- 1-[4-(2-Azepan-1-yl-ethoxy)benzyl]-5-methoxy-2-(4-methoxy-phenyl)-3-methyl-1H-indole (HCl);
2-(4-Ethoxyphenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol or a pharmaceutically acceptable salt thereof;
5
1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-2-(4-ethoxy-phenyl)-3-methyl-1H-indol-5-ol or a pharmaceutically acceptable salt thereof;
10
4-[5-Fluoro-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-2-yl]-phenol (HCl);
1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-3-methyl-2-phenyl-1H-indol-5-ol (HCl);
15
2-(4-Hydroxy-phenyl)-3-methyl-1-[4-(2-pyrollidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol or a pharmaceutically acceptable salt thereof;
1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol (HCl);
20
1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol Acetate Salt;
1-[4-(2-Azocan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol or a pharmaceutically acceptable salt thereof;
25
2-(4-Hydroxy-phenyl)-3-methyl-1-[4-(2-dimethyl-1-yl-ethoxy)-benzyl]-1H-indol-5-ol or a pharmaceutically acceptable salt thereof;
2-(4-Hydroxy-phenyl)-3-methyl-1-[4-(2-diethyl-1-yl-ethoxy)-benzyl]-1H-indol-5-ol or a pharmaceutically acceptable salt thereof;
30
1-[4-(2-Dipropylamino-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol or a pharmaceutically acceptable salt thereof;
1-[4-(2-Dibutylamino-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol or a pharmaceutically acceptable salt thereof;
35
1-[4-(2-Diisopropylamino-cthoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol or a pharmaceutically acceptable salt thereof.;
1-[4-[2-(Butyl-methyl-amino)-ethoxy]-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol or a pharmaceutically acceptable salt thereof;
40
2-(4-Hydroxy-phenyl)-3-methyl-1-[4-[2-(2-methyl-piperidin-1-yl)-ethoxy]-benzyl]-1H-indol-5-ol or a pharmaceutically acceptable salt thereof;
2-(4-Hydroxy-phenyl)-3-methyl-1-[4-[2-(3-methyl-piperdin-1-yl)-ethoxy]-benzyl]-1H-indol-5-ol or a pharmaceutically acceptable salt thereof;
45
2-(4-Hydroxy-phenyl)-3-methyl-1-[4-[2-(4-methyl-piperidin-1-yl)-ethoxy]-benzyl]-1H-indol-5-ol (HCl);
1-[4-[2-(3,3-Dimethyl-piperidin-1-yl)-ethoxy]-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol or a pharmaceutically acceptable salt thereof;
50
1-[4-[2-((cis)-2,6-Dimethyl-piperidin-1-yl)-ethoxy]-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol or a pharmaceutically acceptable salt thereof;
2-(4-Hydroxy-phenyl)-1-[4-[2-(4-hydroxy-piperidin-1-yl)-ethoxy]-benzyl]-3-methyl-1H-indol-5-ol or a pharmaceutically acceptable salt thereof;
55
(1S,4R)-1-[4-[2-(2-Aza-bicyclo [2.2.1] hept-2-yl)-ethoxy]-benzyl]-2-(4-hydroxyphenyl)-3-methyl-1H-indol-5-ol

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or a pharmaceutically acceptable salt thereof;

5 2-(4-Hydroxy-phenyl)-3-methyl-1-[4-[2-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-ethoxy]-benzyl]-1H-indol-5-ol or a pharmaceutically acceptable salt thereof;

10 2-(4-Fluoro-phenyl)-3-methyl-1-[4-(2-piperidine-1-yl-ethoxy)-benzyl]-1H-indol-5-ol (HCl);

15 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-2-(4-fluoro-phenyl)-3-methyl-1H-indol-5-ol or a pharmaceutically acceptable salt thereof;

20 2-(3-Methoxy-4-hydroxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol (HCl);

25 2-Benzo[1,3]dioxol-5-yl-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol (HCl);

30 2-(4-Isopropoxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol (HCl);

35 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-2-(4-isopropoxy-phenyl)-3-methyl-1H-indol-5-ol (HCl);

40 2-(4-Cyclopenyloxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol or a pharmaceutically acceptable salt thereof;

45 3-Methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-2-(4-trifluoromethyl-phenyl)-1H-indol-5-ol or a pharmaceutically acceptable salt thereof;

50 3-Methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-2-p-tolyl-1H-indol-5-ol or a pharmaceutically acceptable salt thereof;

55 2-(4-Chloro-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol (HCl);

60 2-(2,4-Dimethoxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol or a pharmaceutically acceptable salt thereof;

65 2-(3-Hydroxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1 H-indol-5-ol or a pharmaceutically acceptable salt thereof;

70 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-2-(3-hydroxy-phenyl)-3-methyl-1H-indole-5-ol or a pharmaceutically acceptable salt thereof;

75 which is 2-(3-Fluoro-4-hydroxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol or a pharmaceutically acceptable salt thereof;

80 2-(3-Fluoro-4-hydroxy-phenyl)-3-methyl-1-[4-(azepan-1-yl-ethoxy)-benzyl]-1H-indol-5-ol or a pharmaceutically acceptable salt thereof;

85 2-(3-Methoxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-cthoxy)-benzyl]-1H-indole-5-ol or a pharmaceutically acceptable salt thereof;

90 3-Methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-2-(4-trifluoromethoxy-phenyl)-1H-indole-5-ol or a pharmaceutically acceptable salt thereof;

95 3-Chloro-2-(4-hydroxy-phenyl)-1-[4-(2-pyrrolidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol (HCl);

100 3-Chloro-2-(4-hydroxy-phenyl)-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol (HCl);

105 3-Chloro-2-(4-hydroxy-phenyl)-1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-1H-indol-5-ol (HCl);

110 3-Chloro-2-(4-hydroxy-2-methyl-phenyl)-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol or a pharmaceutically acceptable salt thereof;

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- 2-(4-Hydroxy-phenyl)-3-ethyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol (HCl);

5-Hydroxy-2-(4-Hydroxy-phenyl)-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole-3-carbonitrile (HCl);

5-Benzyl-1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-5-hydroxy-2-(4-hydroxy-phenyl)-1H-indole-3-carbonitrile (HCl);

5-Benzyl-1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-5-hydroxy-2-(4-hydroxy-phenyl)-1H-indole or a pharmaceutically acceptable salt thereof;

Dipropionate of 1-[4-(2-Azepan-1-yl-ethoxy)benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol (HCl);

Di-pivalate of 1-[4-(2-Azepan-1-yl-ethoxy)benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol (HCl);

5-Benzyl-1-[4-(3-piperidin-1-yl-propoxy)-benzyl]-3-methyl-1H-indole or a pharmaceutically acceptable salt thereof;

2-(4-Hydroxyphenyl)-3-methyl-1-[4-[3-(piperidin-1-yl)-propoxy]benzyl]-1H-indol-5-ol or a pharmaceutically acceptable salt thereof;

2-(4-Hydroxyphenyl)-1-[3-methoxy-4-(2-piperidin-1-yl-ethoxy)benzyl]-3-methyl-1H-indol-5-ol or a pharmaceutically acceptable salt thereof;

2-(4-Hydroxyphenyl)-1-[3-methoxy-4-(2-azepan-1-yl-ethoxy)benzyl]-3-methyl-1H-indol-5-ol or a pharmaceutically acceptable salt thereof;

5-Benzyl-1-[4-(3-Methoxy-4-(2-piperidin-1-yl-ethoxy)benzyl)-1H-indole or a pharmaceutically acceptable salt thereof;

5-Benzyl-1-[4-(3-Methoxy-4-(2-azepan-1-yl-ethoxy)benzyl)-1H-indole or a pharmaceutically acceptable salt thereof;

Di-pivalate ester of 2-(4-Hydroxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol or a pharmaceutically acceptable salt thereof;

5-Benzyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-3-methyl-1H-indole or a pharmaceutically acceptable salt thereof;

5-Benzyl-1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-3-methyl-1H-indole or a pharmaceutically acceptable salt thereof;

2-(4-Hydroxyphenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol or a pharmaceutically acceptable salt thereof;

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2-(4-Hydroxyphenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)benzyl]-1H-indol-5-ol methiodide;

or

5 2-(4-Hydroxy-phenyl)-3-methyl-1-[4-(2-dimethyl-1-yl-ethoxy)-benzyl]-1H-indol-5-ol methiodide.

10 5. A pharmaceutical composition comprising a compound of Claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

15 6. A method of treating or preventing bone loss in a mammal, the method comprising administering to a mammal in need thereof an effective amount of a compound of Claim 1, or a pharmaceutically acceptable salt thereof.

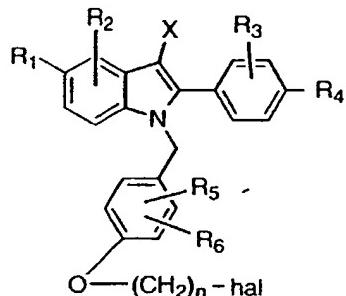
15 7. A method of treating or preventing disease states or syndromes which are caused or associated with an estrogen deficiency in a mammal, the method comprising administering to a mammal in need thereof an effective amount of a compound of Claim 1, or a pharmaceutically acceptable salt thereof.

20 8. A method of treating or preventing cardiovascular disease in a mammal, the method comprising administering to a mammal in need thereof an effective amount of a compound of Claim 1, or a pharmaceutically acceptable salt thereof.

25 9. A method of treating or preventing disease in a mammal which result from proliferation or abnormal development, actions or growth of endometrial or endometrial-like tissue, the method comprising administering to a mammal in need thereof an effective amount of a compound of Claim 1, or a pharmaceutically acceptable salt thereof.

25 10. A process for preparing a compound of formula I which comprises one of the following:

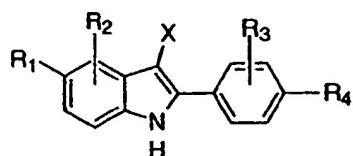
a) reacting a compound of formula



wherein n, R₁-R₆ and X are as defined in Claim 1 and hal is chlorine or bromine with a compound of formula



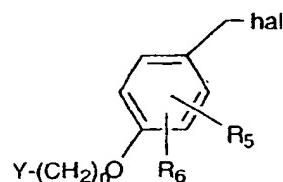
where R₇ and R₈ are as defined in Claim 1 to give a corresponding compound of formula I or II; or
b) reacting a compound of formula



wherein R₁-R₄ and X are as defined in Claim 1 in the presence of a base, e.g NaH, with a compound of formula

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10 wherein n, R₅, R₆ and Y are as defined in Claim 1 and hal is a halogen, e.g Cl or Br to give a corresponding compound of Formula I or II;

if necessary protecting any reactive substituent groups during each process above and removing the same. if desired converting a phenolic group present to a phosphate, sulfate, sulfamate or sulfate ester; and further if desired converting the compound of formula I or II to a pharmaceutically acceptable salt.

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European Patent
Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number

which under Rule 45 of the European Patent Convention EP 97 30 2576
shall be considered, for the purposes of subsequent
proceedings, as the European search report

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
D,A	EP 0 639 567 A (OTSUKA PHARMACEUTICAL FACTORY, INC.) * tables 15,17,19 *	1,5	C07D209/10 A61K31/40 C07D209/12 C07D405/12
D,A	WO 95 17383 A (KARO BIO AB) * claims *	1,5	C07D405/04 C07D209/02
A	WO 93 10741 A (ENDORECHERCHE INC.) * tables 1-3 *	1,5	C07D209/52 C07D209/30 C07D209/42

INCOMPLETE SEARCH			
<p>The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.</p> <p>Claims searched completely :</p> <p>Claims searched incompletely :</p> <p>Claims not searched :</p> <p>Reason for the limitation of the search:</p> <p>See sheet C</p>			
Place of search		Date of completion of the search	Examiner
THE HAGUE		19 June 1997	Van Bijlen, H
CATEGORY OF CITED DOCUMENTS		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document			



INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.

Claims searched completely:

Claims searched incompletely:

Claims not searched: 6-9

Reason for the limitation of the search: Although claims 6-9 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.